A RANDOMIZED (1:1), DOUBLE-BLIND, MULTI-CENTER, PLACEBO CONTROLLED STUDY EVALUATING INTENSIVE CHEMOTHERAPY WITH OR WITHOUT GLASDEGIB (PF-04449913) OR AZACITIDINE (AZA) WITH OR WITHOUT GLASDEGIB IN PATIENTS WITH PREVIOUSLY UNTREATED ACUTE MYELOID LEUKEMIA

Investigational Product Number:	PF-04449913
Investigational Product Name:	Glasdegib
United States (US) Investigational New Drug (IND) Number:	105453
European Clinical Trials Database (EudraCT) Number:	2017-002822-19
Protocol Number:	B1371019
Phase:	Phase 3

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	27-July-2017	Not applicable (N/A)
Amendment 1	19-September-2017	All changes were made prior to start of the study and made per FDA comments except where indicated. Other minor changes were added for clarity. Schedule of Activities for the Intensive and Non-intensive Studies and applied throughout protocol: • For bone marrow assessments, bone marrow aspirates are required; however, we now added preference for bone marrow biopsies in addition to aspirates. In the event of an inadequate aspirate, a bone marrow biopsy is required. • Baseline genetics edits made for clarification that known genetics at the time of randomization will be used to stratify subjects. • Red blood cell and platelet transfusion history required 8 and not 24 weeks prior to randomization for the non-intensive study only. • Added windows for follow-up assessments. Schedule of Activities for the Intensive Study only: • Removed collection of prior transfusions; only collect during study. • Changed from every 28 day to weekly chemistries. • Consolidation with cytarabine changed from 1-3 g/m^2 to 3 g/m^2 for adults <60 years and 1 g/m^2 for adults ≥60 years. • Following HSCT, subjects will not be allowed to have ≥Grade 2 GVHD before resuming glasdegib/placebo. PGIC not collected at baseline for non-intensive study, updated as a correction

Document	Version Date	Summary of Changes and Rationale
		Table 2: Made a correction by adding the time, 1 hour post-dose, for the column labeled "Glasdegib following chemotherapy". Cycle ≥1, Day 1 Secondary Endpoint (Section 2 and throughout protocol): added CR with partial hematologic recovery (CRh) for the Non-intensive study only. CCI [redacted] Inclusion Criterion 5: removed one single dose of Ara C of up to 2 grams for control of blasts counts. Exclusion Criterion 10: clarified that dose equivalent of ≥550 mg/m^2 of daunorubicin is a criterion for the Intensive Chemotherapy study only. Dose Modifications (Section 5.5.5): clarified glasdegib or placebo does not be delayed or dose reduced for Grade 3/Grade 4 non-hematologic, study-treatment-related toxicity and should be permanently discontinued if interruptions are for more than 28 consecutive days. Concurrent administration of herbal preparations prohibited (Section 5.8.1), added as a clarification since it is already an exclusion criterion. Prophylactic Intrathecal Chemotherapy allowed per investigator discretion in Permitted Concomitant Medications in Section 5.8.2. Efficacy Assessments (Section 7.2) now includes definition for CR with partial hematologic recovery for the Non-intensive study. Immunophenotying and Genetics (Section 7.2.2) clarifications added regarding requirement to stratify based on known genetic risk classification at the time of randomization. Section 9.3.2: Added updated definitions for EFS and includes CR/CRh as response (in duration of response and time to response endpoints) for the non-intensive study. CCI [redacted]

Document	Version Date	Summary of Changes and Rationale
		Appendix 4: Added response definition for CRh and clarified CRi requires either criteria for residual neutropenia or thrombocytopenia must be met. Appendix 14: added ELN Risk Stratification by Genetics table. General spelling and grammar issues corrected. CCI [redacted]

Amendment 2	15-November -2017	All changes were made prior to start of the study in response to FDA request except where indicated. Other minor changes were added for clarity.
		
		Secondary endpoints updated:
		
		• CR/CRh was added to duration of response assessment to match statistical analysis section.
		
		• CR/CRh was added to time to response assessment to match statistical analysis section.
		
		• Schedule of Activities (Intenstive study):
		
		  • Pregnancy testing added for Day 1 of each Consolidation Cycle with single-agent cytarabine and Day 1 of each cycle where single-agent glasdegib/placebo administered to ensure appropriate safety monitoring.
		
		• Schedule of Activities (Intenstive and Non-intensive studies):
		
		  • Immunophenotyping was removed because it is not required for any study analysis. Immunophenotyping was also removed from Sections 7.1 and 7.2.2 for consistency.

Document	Version Date	Summary of Changes and Rationale

		• X's added to tables so tables now match footnotes indicating specified instances AEs and SAEs may be collected during the follow-up period.
		
		• Table 2 and Table 4 now provide time windows for assessments allowing sites flexibility in obtaining assessments without jeopardizing data.
		
		• Other minor footnote clarifications to ensure consistency with tables.
		
		• Inclusion Criterion #4: removed bullet indicating that the criterion does not apply to subjects with bundle branch blocks and is otherwise asymptomatic. This conflicted with an exclusion criterion and was confusing.
		
		• Exclusion Criterion #4: specified that a subject could not participate in other clinical studies involving other investigational drugs to clarify that this did not apply to glasdegib in this study.
		
		• Section 5.4.1.2: Reduced the text describing the azacitidine supply to match information supplied for other chemotherapy drugs in this study. Edits added for clarity, instructing sites to follow local regulations.
		
		• Section 5.5.5 updated per FDA request to provide more information regarding glasdegib/placebo dose modifications.
		
		  • Corrected typographical error in Section 5.5.5.1 indicating that glasdegib or placebo does not need to be delayed or dose reduced for hematologic, study-treatment-related toxicity.
		
		  • Specified dose escalations will not be allowed following glasdegib/placebo dose reductions.
		
		  • Added Section 5.5.5.2 for dosing interruptions for glasdegib/placebo non-hematological toxicities.

Document	Version Date	Summary of Changes and Rationale
		• Section 5.8.1: corrected a typographical error, removing word permitted. Section 7.1.3: Added text specifying that assessment of acute GVHD will be graded by standard criteria based on the Consensus conference on acute GVHD grading and assessment of chronic GVHD will be assessed based on the NIH criteria with associated references. Grading and Staging for acute GVHD is summarized in Appendix 15. • Section 7.1.4: Clarified that laboratory tests only need to be obtained during screening, and there is no need to repeat these tests on Day 1 if performed within 3 days prior to randomization. • Section 7.1.7: specified type of ECGs (supine) for clarity. • Section 7.4.3 updated per FDA request: • Changed PGIS from 7-point scale to a 4-point scale. The FDA recommended that Pfizer revise the PGIS to 4-response options (eg, absent (no symptoms), mild, moderate, and severe) so patients can easily distinguish severity. • Section 9.2.5: updated for clarity; now specifies Intensive and Non-intensive studies. • Section 9.3.2: updated per FDA request, specifying type of analysis required for fatigue and to correct minor errors. C C I [redacted] • For the Non-intensive study, Method 2 for the EFS definition now specifies CR or CRi will be evaluated following up to 6 cycles of therapy. • Now specifies the Brookmeyer and Crowley method will be used to evaluate EFS for clarity.

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		• PK Parameters now specify C_{trough} will be reported for glasdegib metabolites, if relevant. Though there is no activity anticipated for the N-desmethyl metabolite (M3) that is <10% in circulation; possible metabolite measurement is added, if applicable as a conservative approach.
		
		• Appendix 4 updated to match data analysis section for consistency:
		
		  • Absence of CRh added to SD definition.
		
		  • Treatment failure definitions added for Intensive and Non-intensive studies.
		
		• Appendix 11 updated to address FDA comments:
		
		  • PGIS now includes question regarding leukemia symptoms.
		
		General spelling, grammar, and consistency issues corrected throughout the protocol.

Amendment 3	1-March-2018	All changes were made prior to start of the study in response to regulatory requests except where indicated. Other minor changes were added for clarity. Addded BRIGHT AML1019 study logo to cover page. Endpoints: clarified response definition by defining CRi or better to include CR (including CRMRD-negative) or CRi for intensive chemotherapy subjects, and CR (including CRMRD-negative), CRh, or CRi for non-intensive chemotherapy subjects. CRh or better is only defined for non-intensive chemotherapy subjects as CR (including CRMRD-negative) or CRh. Also updated Section 9.3 (and subsections) and Appendix 4 with these definitions. Schedule of Activities: • Clarified that bone marrow assessments for study assessments other than disease classification must be done after informed consent signed in footnotes, as specified in the Protocol Administrative Change

Document	Version Date	Summary of Changes and Rationale
		Letter, dated 20 Dec 2017. • Added whole blood collection for immunophenotyping and molecular profiling on Day 1, prior to dosing study drug to provide a baseline sample to compare to future samples for MRD assessment. • Removed whole blood collection for pharmacogenomic analysis from intensive and non-intensive chemotherapy studies because pharmacogenomic analysis of drug metabolizing enzymes and transporters was no longer a priority for this study as it was unlikely to provide valuable information that would inform either safety or efficacy. Also removed Section in protocol defining this analysis. • Added additional times when bone marrow samples must be collected post consolidation for the Intensive Study so MRD status may be confirmed in a timely manner. • Table 3: blood chemistry deleted from follow-up visits; added in error. Section 1.2.3: Edited text for glasdegib nonclinical toxicity to align with updated data. Inclusion criterion #5: specified anti-cancer agents for clarity in response to regulatory request. Exclusion criteria #7: removed right bundle branch blocks as this is common and it should not be excluded. Section 4.3.1: Added a requirement for a backup contraception method in response to regulatory request. Section 5.4.1.3: removed subcutaneous route for cytarabine since this will not be an option. Removed term *allogeneic* because either autologous or allogeneic HSCT is allowed during the Intensive Chemotherapy Study per regulatory feedback.

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		Section 5.8.1: re-organized CYP3A4/5 inducers so bullet appears under proper heading. Table 11 now specifies that glasdegib/placebo should be permanently discontinued for all cases of confirmed DILI/Hy's Law and potential cases require glasdegib/placebo dose interruption and potential restarting. Added in response to regulatory request. Table 14 now includes required bicarbonate testing to determine dose reductions per azacitidine label, per regulatory request. Also clarified indication for U/A with microscopic evaluation and 24-hour urine protein. Sections 7.1.7: removed additional QTc monitoring requirements if a moderate/strong CYP3A4/5 inhibitor or TdP drug administered during study since additional monitoring was not required. Section 9.3: Changes in the PRO section were made to improve clarity regarding planned analyses per regulatory request. Other changes clarified method by which response will be analyzed. Removed section specifying end of trial in a member state because LSLV will be considered the end of trial in all participating countries. Removed due to regulatory request. Appendix 16 added per country-specific requirement in France. General spelling, grammar, and consistency issues corrected throughout the protocol.
Amendment 4	02-July-2018	Amendment 4 changes will be applicable to subjects enrolling in Germany. German ethics committee requested collection of unrelated SAEs during the HSCT period. This edit was made in Section 8.1. Section 9.5.1: deleted text impacted by update to Section 8.1.

Document	Version Date	Summary of Changes and Rationale
Amendment 5	12 April 2019	Note that 2 tables have been removed from the introduction section, resulting in updated table numbers. Schedule of Activities (SOA): Tables 1 and 3, Footnote 1: clarify that assessments performed as standard of care within 28 days of randomization do not need to be repeated to be used for screening. Tables 1 and 3, Footnote 4: clarified that Response Assessment includes assessment of EMD (eg, disease in CSF). Table 1, Footnotes 6 and 7: clarified that weekly hematology and chemistry tests must continue weekly until the next phase of study/treatment begins. Table 1, Footnote 14 and Table 3, Footnote 13: Morning dosing of blinded therapy is preferred but not mandatory, rationale for change added to Section 5.5.1.1. Tables 1 and 3, Deleted individual rows for each Patient Reported Outcome survey since they are administered together and are outlined in footnote and Section 7.4. Table 1, Footnote 32 and Table 3, Footnote 36: added “if able” to the PRO collection during HSCT period. Table 3 and Section 5.5.1.3: Subjects enrolled in the Non-Intensive study may undergo HSCT per local standard of care and at the Investigator’s discretion. Table 1, Footnotes 26, 27, 38 and Table 3, Footnotes 24, 25, 31: Updated with text related to China samples. Table 1, Footnote 19, Table 3, Footnote 16 and Section 7.2.3: Bone marrow assessments within 3 weeks of growth factor administration are evaluable and do not need to be repeated. Original text that these BM assessments would not be considered evaluable has been deleted. Introduction: Background (Section 1.2) and Rationale sections have been separated and updated to reflect current

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		data and Investigator Brochure (IB). • Removed Nonclinical Toxicology text (Section 1.2.3). • Clinical Development (Section 1.2.4): Removed Table 5 and Table 6. Safety and Efficacy sections removed and new section inserted describing Glasdegib Clinical Pharmacology. Updates to relevant clinical studies with glasdegib made to provide relevant background. Data from thorough QTc study included. Section 4.2, Inclusion/Exclusion: • Inclusion #1: Clarified that subjects with FLT3+ AML not receiving and not intended to receive a FLT3 inhibitor during study participation are allowed per regulatory agreement. • Inclusion #5: Removed ATRA since it is meant to treat APL and removed anageride. Text added, continuation or resumption of hydroxyurea or leukopheresis after described time period must be approved by the Sponsor. • Exclusion #1: Clarified that APL is associated with t(15;17). • Exclusion #2: Clarified that the mutation must be known. • Exclusion #4: QTc exclusion does not apply to subjects with cardiac pacemaker. • Exclusion #14: Removed local radiation as an excluded treatment modality during the screening period. Section 4.3: Text added defining Screen Failures as subjects who consent to participate in the clinical study but are not subsequently randomized. Added data collection required for Screen Failure subjects. Section 4.4.1: Text updated to require one method of birth

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		control, consistent with sponsor requirements. Language added to to clarify Investigator responsibility for reproductive capability assessment. Table 6: Updated to include abstinence. Section 4.4.2: Added to provide postmenopausal definition. Section 5.2 Breaking the Blind: Text now reflects that CRF does not collect Break blind data, but that this will be documented within the source. Additionally, subjects may not continue on study treatment once an investigator breaks the blind for that subject. Section 5.5.1.2: Clarification text added regarding the timing and terms of bone marrow assessments. Section 5.5.2: Adverse events and concomitant medications will not be collected during long-term follow-up. Table 10 Glasdegib/placebo Dose Modifications for mean QTcF Prolongation: updated in alignment with the US Package Insert (USPI) Also added comment that mQTcF dose mods do not apply to subjects with cardiac pacemakers. Figure 2: Updated for clarity and to align terms with CRF fields. Figure 3: Updated with addition of option for HSCT. Section 5.8.1: Removed requirement of discussion with Medical Monitor for the concomitant use of CYP3A4 inhibitors/inhibitors. Section 5.8.2.2: Removed text requiring a repeat BM assessment if done within 3 weeks from last dose of growth factor. Growth factors may be given per local standard of care and local label. Section 6.4, Table 1, Footenote 31 and Table 3, Footnote 29: Text added regarding the use of public records for long term survival follow-up as allowed by

Document	Version Date	Summary of Changes and Rationale
		local law. Section 7.2.1: Additional text describing the AML response assessment added for clarity. Section 7.2.2: Text added allowing post baseline genetic assessments to be limited to abnormalities noted at baseline and molecular assessments to follow standard of care. CCI [redacted] [redacted] Section 7.4: Updates to account for hospitalized subject schedules, subjects with visual problems, and clarification that for patients hospitalized or with a timepoint falling on a weekend or holiday, PRO questionnaires may be performed on the next business day. Section 7.1.4: Re-screening is allowed. Section 9: • 9.1: clarified percentage of patients censored for OS used in the sample size determination. • 9.2: clarified all analyses of intensive and non-intensive chemotherapy subjects will be conducted separately and independently of each other. • 9.3.1: added region (rest of world versus China) as a stratification factor to the primary and secondary analyses for intensive patients due to potentially different rates of stem cell transplantation. • 9.3.2: clarified all secondary PRO and efficacy endpoints will be based on the full analysis set unless stated otherwise; clarified method for calculating confidence intervals for binary efficacy endpoints; removed Kaplan-Meier analysis for time to response as analysis is for responders only; clarified censoring for those without event-free

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		survival events; clarified which event-free survival methods are for responders only. • 9.4: clarified transfusion conversion rate is analyzed in the safety analysis set. • 9.5.1: clarified safety analyses are analyzed in both intensive and non-intensive studies. • 9.7: clarified DMC will convene at least once yearly per DMC charter. Clarified throughout document that restarting glasdegib/placebo Post HSCT requires no **ongoing** ≥Grade 2 graft-versus-host disease (GVHD). Section 14: Added text regarding options for Non-Intensive subjects to continue treatment at study end. Appendix 1: Added abbreviation for HGRAC. Appendix 4: Updates for clarity and readability. Appendices 5, 6, 7, 8 and references updated. General spelling, grammar, repetitions and formatting corrected.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Indications

Glasdegib is being studied in combination with azacitidine for the treatment of adult patients with previously untreated acute myeloid leukemia (AML) who are not candidates for intensive induction chemotherapy (Non-intensive AML population).

Glasdegib is being studied in combination with cytarabine and daunorubicin for the treatment of adult patients with previously untreated acute myeloid leukemia (Intensive AML population).

Background and Rationale

Glasdegib is a selective, orally administered inhibitor of smoothened (SMO), which demonstrates potent and selective inhibition of Hedgehog (Hh) signaling in vitro and significant antitumor efficacy in vivo. The Hh signaling pathway regulates cell differentiation and self-renewal in the developing embryo, and is typically silenced in adult tissues. Aberrant Hh signaling may result from mutations in key pathway genes, non-mutational mechanisms related to the secretion of Hh ligands, or from cells in the tumor microenvironment. Aberrant Hh signaling has been identified in a variety of human leukemia and leukemic stem cells (LSCs).[1-3] Upregulation of Hh pathway components has been observed in chemo resistant AML cell lines in vitro, and pharmacological inhibition of the Hh pathway resulted in decreased multi-drug resistance 1 (MDR-1) or P-glycoprotein (P-gp) expression in these cells.[4] The SMO inhibitors, vismodegib (Erivedge®)[5] and sonidegib (Odomzo®)[6] have been demonstrated to be safe and effective in the treatment of patients with advanced basal cell carcinoma. Glasdegib is being developed for indications in myeloid malignancies.

Acute Myeloid Leukemia (AML) is a heterogeneous cancer of the hematopoietic system characterized by increased blast counts, pancytopenias causing infections and bleeding, and reduced survival. AML is characterized by multiple genetic mutations at the time of diagnosis that evolve with treatment, resulting in treatment resistance, disease relapse, and reduced survival. It is estimated that there will be 21,380 new cases and 10,590 deaths from AML in the United States (US) in 2017.[7] Incidence rates in Europe are similar to rates in the United States.[8] AML is a disease of older people and is uncommon before the age of 45. The average age of a patient with AML is about 67 years.

Existing standards of care, such as anthracycline + cytarabine or hypomethylating agents like decitabine and azacitidine, can induce complete remissions in 5-70% of patients; however, remissions are not durable and disease relapse occurs in up to 60% of patients.[9] For AML patients unable to receive intensive chemotherapy, existing standard treatments like low-dose cytarabine (LDAC) are associated with response rates <20% and median overall survival (mOS) times of 5-6.5 months. Hypomethylating agents, although not approved in the US specifically for AML, have shown improved overall survival (OS) vs LDAC in AML patients not suitable for intensive chemotherapy. Midostaurin (Rydapt®) is indicated for use in combination with standard '7+3' cytarabine and daunorubicin induction, and with cytarabine consolidation therapy, for the treatment of adult patients with newly diagnosed AML who are

FLT3 mutation-positive. Approval in 2017 was based on the Phase III RATIFY (Cancer and Leukemia Group B [CALGB] 10603) clinical trial resulting in a 23% reduction in the risk of death compared with chemotherapy alone (hazard ratio [HR] = 0.77, 95% confidence interval [CI], 0.63, 0.95; 2 sided p=0.016).[10] Event-free survival (EFS) was significantly higher for Rydapt plus chemotherapy versus chemotherapy alone (EFS median of 8.2 months compared to 3.0 months, HR = 0.78, 95% CI 0.66, 0.93 and 2 sided p=0.004). The most frequent adverse events (AEs) were febrile neutropenia, nausea, vomiting, mucositis, headache, musculoskeletal pain, petechiae, device-related infection, epistaxis, hyperglycemia and upper respiratory tract infections.

Reducing the incidence of disease progression to prolong survival remains the highest unmet medical need in the treatment of AML patients.[11-13]

Glasdegib has shown activity in myelodysplastic syndrome (MDS) and AML with improved response rates and improved OS.

In the safety lead-in cohort of the B1371012 study, 12 patients with previously untreated intermediate-2 or high-risk MDS (n=7) AML with 20-30% blastsand multi-linage dysplasia (n=3), erythroleukemia (n=1) or CMML (n=1) were treated with glasdegib in combination with azacitidine. Patients were treated for a median 94.0 days. One patient had a glasdegib dose reduction 98 days after start of treatment. As of March 2017, 5 out of the 12 patients responded. 3 patients with CR (all AML) and 2 patients with marrow CR.[14] The number of CRs observed with glasdegib and azacitidine appears favorable in the context of the 15-17% CR rate seen with azacitidine alone.

In the randomized Phase 2 cohort of Study B1371003, patients with previously untreated AML or high-risk MDS who were not candidates for standard induction chemotherapy using established criteria[15] were stratified into good/intermediate risk vs poor risk by genetics and were randomized 2:1 to receive in an open-label fashion, LDAC + glasdegib vs LDAC alone. In AML patients (78 and 38 randomized to LDAC + glasdegib and LDAC, respectively), mOS for LDAC + glasdegib was 8.3 vs 4.3 months for LDAC alone (and OS HR=0.463, with p-value=0.0002) with 94 observed deaths. Glasdegib has demonstrated a statistically significant and clinically meaningful improvement in OS when combined with LDAC vs LDAC alone in elderly AML patients not suitable for intensive chemotherapy, with no new significant safety signals identified to date in a prospective randomized trial.

In the ongoing single-arm Phase 2 cohort of Study B1371003, patients with previously untreated AML or high-risk MDS received intensive chemotherapy (‘7+3’) in combination with glasdegib in an open-label fashion. The ‘7+3’ regimen consists of 7 days of cytarabine and 3 days of daunorubicin. Based on investigator’s assessment, CR rate for AML patients was 47% (80% CI 38.3-55.6) and Complete Remission/Complete remission with incomplete hematologic recovery (CR/CRi) rate was 55% (80% CI 46.7-62.7). The mOS for AML pts (n=64) was 16.3 months with 37 observed deaths.

Based on results from B1371003, 2 prospective randomized (1:1), double-blind, placebo controlled registration trials in patients with newly diagnosed AML are proposed: in the first study, 400 AML patients suitable for intensive chemotherapy will be randomized to receive '7+3'+ glasdegib (Arm A) or '7+3'+ placebo (Arm B). In the second study, 320 AML patients not suitable for intensive chemotherapy per investigator will be randomized to receive azacitidine + glasdegib (Arm A) or azacitidine + placebo (Arm B). The primary endpoint for both trials will be OS. Both studies will be powered, conducted, and analyzed separately and independently under 1 protocol (B1371019) to maximize efficiency. Together, the trials can provide substantial evidence to register glasdegib in AML patients treated in combination with 7+3 or with azacitidine.

Objectives and Endpoints

Protocol B1371019 consists of 2 independent studies: an intensive chemotherapy study and non-intensive chemotherapy study. Within each study, subjects will be randomized to chemotherapy with either glasdegib or matching placebo. The primary and secondary endpoints for each study will be analyzed separately. Response criteria for AML are defined by the 2017 European LeukemiaNet (ELN) recommendations.[16]

The objectives and endpoints for each study are the same unless otherwise specified and are described below:

Primary Objective:	**Primary Endpoint:**
• To demonstrate that glasdegib is superior to placebo in combination with azacitidine (non-intensive study) or cytarabine and daunorubicin (intensive study) in prolonging OS in subjects with untreated AML.	• Overall survival.
Secondary Objectives:	**Secondary Endpoints:**
• To compare fatigue score post-baseline as measured by MDASI-AML/MDS in both treatment arms; • To compare glasdegib versus placebo in combination with azacitidine (non-intensive study) or '7+3' (cytarabine and daunorubicin) in improving other clinical efficacy measures; • To estimate the duration of response in both treatment arms; • To estimate the time to response in both treatment arms in the Non-intensive study only; • To compare Event-free Survival (EFS) in both treatment arms; • To compare PRO measurements in both	• Fatigue score measured by the MDASI-AML/MDS questionnaire; • Rate of CR (including $CR_{MRD\text{-}negative}$ as assessed by multiparametric flow cytometry), CRi as defined by the ELN recommendations (2017), MLFS, PR, and CR with partial hematologic recovery (CRh) for the Non-intensive study only; • Duration of response (defined as CRi or better or CRh or better if applicable)*; • Time to response (CRi or better or CRh or better)* in the non-intensive study only; • Event-free Survival; • PROs as measured by the M.D. Anderson Symptom Inventory AML/MDS Module

treatment arms; • To evaluate the overall safety profile in both treatment arms; • To evaluate laboratory abnormalities in both treatment arms; • To characterize the pharmacokinetics (PK) of glasdegib; • To characterize treatment effects on the QTc interval.	(MDASI-AML/MDS), EuroQoL 5 Dimension questionnaire 5-Level version (EQ-5D-5L), Patient Global Impression of Symptoms (PGIS) and Patient Global Impression of Change (PGIC); • Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; • PK of glasdegib; • QTc interval.
CCI [redacted]	[redacted]
[redacted]	[redacted]

* CRi or better includes CR (including $CR_{MRD\text{-}negative}$) or CRi for intensive chemotherapy subjects, and CR (including $CR_{MRD\text{-}negative}$), CRh, or CRi for non-intensive chemotherapy subjects. CRh or better is only defined for non-intensive chemotherapy subjects as CR (including $CR_{MRD\text{-}negative}$) or CRh.

Study Design and Study Treatment

Intensive Chemotherapy Study:

A total of 400 subjects eligible to receive intensive chemotherapy per investigator assessment will receive treatment as follows:

- Experimental Therapy: Glasdegib 100 mg orally (PO), once a day (QD) or matching placebo will be administered PO QD, starting Day 1 of chemotherapy. Subjects will receive daily glasdegib 100 mg PO or matching placebo for up to 2 years after randomization or until CR with minimal residual disease (MRD)-negative disease status is documented post consolidation or HSCT based on confirmed central laboratory results. Glasdegib or placebo therapy may continue throughout induction(s) and consolidation therapy regardless of any delays/modifications in the chemotherapy treatment.

    - For subjects proceeding to hematopoietic stem cell transplantation (HSCT) post remission during the study period, glasdegib or placebo will be interrupted at least 28 days before HSCT Day 0 and resumed 30-60 days post date of stem cell infusion, once there is absolute neutrophil count (ANC) engraftment, no ongoing ≥ Grade 2 graft-versus-host disease (GVHD) and no ongoing serious adverse events (SAEs) that prevent resuming glasdegib or placebo in the judgement of the investigator.

- '7+3' Induction: cytarabine 100 mg/m^2 intravenous (IV) daily by continuous infusion for 7 days (Days 1-7) plus daunorubicin 60 mg/m^2 IV daily × 3 days.

- If a second induction is needed, Investigators will select either '5+2' (cytarabine 100 mg/m^2 IV daily by continuous infusion × 5 days plus daunorubicin 60 mg/m^2 IV daily × 2 days) or repeat '7+3'.

- If <5% bone marrow blasts: Consolidation may include either or both of the following:

    - Consolidation with single-agent cytarabine 3 grams (g)/m^2 IV for adults <60 years and 1 g/m^2 for adults ≥60 years over 3 hours twice daily (BID) on Days 1, 3, and 5, every 28 days for up to 4 cycles or alternative single-agent cytarabine dosing schedules may be used per local prescribing information.

    - HSCT administered per local standard of care.

Following Chemotherapy or HSCT, glasdegib or matching placebo may be permanently discontinued as described in Section 6.5. Subject will discontinue blinded therapy if disease status is MRD-negative post consolidation or HSCT by 2 consecutive timepoints per central laboratory results. Subjects will then enter the post treatment follow-up phase for survival assessments.

Non-Intensive Chemotherapy Study

A total of 320 patients who are not considered adequate candidates to receive or who refuse intensive chemotherapy will be treated as follows:

- Experimental therapy: Glasdegib 100 mg PO QD or matching placebo. Both will be administered daily, starting on Day 1 and will continue if subjects demonstrate reasonable evidence of clinical benefit and do not meet the criteria for progression regardless of any delays/modifications in the chemotherapy treatment. Subjects will continue glasdegib or placebo until disease progression, unacceptable toxicity, consent withdrawal, or death, whichever comes first. If there is HSCT per local standard of care, single agent blinded therapy may be administered up to 2 years post randomization or until they have 2 consecutive CR MRD negative central laboratory results, whichever comes first.

    - For subjects proceeding to HSCT following CR during the study period, glasdegib or placebo will be interrupted at least 28 days before HSCT Day 0 and may be resumed 30-60 days post date of stem cell infusion, once there is ANC engraftment, no ongoing ≥ Grade 2 graft-versus-host disease (GVHD), and no ongoing SAEs that prevent resuming glasdegib or placebo in the judgement of the investigator.

- All subjects will receive azacitidine per local label or per the Investigational Product Manual (or summary of product characteristics [SPC]). The dose for azacitidine is 75 mg/m^2 daily for 7 days administered by subcutaneous (SC) injection or IV infusion in 28 day cycles.

- Alternate dosing schedule to administer the 7 doses may be used to accommodate patient and treatment center availability. Dose adjustments will be made according to institutional guidelines or per the SPC for azacitidine. In addition, each subsequent cycle may be delayed for up to 28 days to allow for recovery of blood counts.

- Subjects who proceed to HSCT will not receive azacitidine post HSCT.

Discontinuation of Study Therapy for the Non-Intensive Study

If glasdegib or placebo is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal, single-agent treatment with azacitidine may be continued if, in the Investigator's judgment, a clinical benefit has been observed.

In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study treatment and entered into the follow-up phase of the study.

Statistical Methods

Sample Size Determination

The interim and final analyses of the intensive chemotherapy and non-intensive chemotherapy populations will be conducted separately and independent of each other.

Intensive Chemotherapy Study:

Approximately 400 subjects are to be enrolled with 33% expected to be censored. A total of 267 death events among the enrolled subjects would provide 90% power to detect an improvement in OS with an HR of 0.67 (translating in mOS from 21 months to 31.5 months assuming a composite mOS for the population as follows: young AML [aged ≤60 years] with a mOS of 23.7 months and elderly AML [aged >60 years] with a mOS of 15 months[17,18]) using a 1-sided log-rank test at a significance level of 0.025 and a 3-look group-sequential design.

Two interim analyses would be conducted: an early futility-only analysis of OS after 50% death events occur and an efficacy and futility analysis of OS after 70% deaths occur in the Intensive Chemotherapy population or upon completion of enrollment of these patients, whichever occurs later.

Non-Intensive Chemotherapy Study:

Approximately 320 subjects are to be enrolled with 31% expected to be censored. A total of 220 death events among all the enrolled subjects would provide 90% power to detect an improvement in OS with an HR=0.64 (translating in mOS from 10.4 months[9] to 16.2 months) using a 1-sided log-rank test at a significance level of 0.025 and a 2-look group-sequential design. One interim efficacy and futility analysis of OS would be planned after 60% death events occur in the non-intensive chemotherapy population or upon completion of enrollment of these patients, whichever is later.

SCHEDULE OF ACTIVITIES

The Schedule of Activities tables provide an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Schedule of Activities for Patients Receiving Intensive Chemotherapy: Glasdegib/Placebo + Cytarabine/Daunorubicin

	Screening	Induction					Consolidation Cytarabine and/or post remission HSCT[17]							Following Consolid-ation(s)[36]: up to 2 years post randomization	Post Treatment		
		Induction 1 and Induction 2					Cytarabine[16] 1-4 Cycles (28-day cycle)				HSCT period[34,37]			28-day cycle			
Protocol Activity	**≤28 days prior to study entry**	**Day 1**	**Every 7 days (±2 days)**	**Every 28 days** (±2 days)	**Post first Induc-tion**	**Remis-sion Assess-ment**	**Day 1**	**Day 5**	**Day 10 (±1 days)**	**Day 21** (±7 days)	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**Day 1 (±2 days)**	**End of Treatment** Visit[29] (Within 14 days after last dose)	**Post Treat_ment Follow-Up Visits (±7 days)**[30]	**Long- Ter m Follow-Up Activity Log (±14 days)**[31]
Baseline documentation																	
Informed Consent[1]	X																
Medical History[2]	X																
ECOG Performance Status[3]	X	X					X							X	X		
Disease Classification[4]	X																
Physical Examination[5,30]	X	X		X		X	X		X	X				X	X	X	
HSCT- related information[34]											X			X			
Laboratory Studies																	
Hematology[6,30]	X	X	X		X	X	X	X	X	X				X	X	X	
Blood Chemistry[7]	X	X	X		X	X	X	X	X	X				X	X		
Urinalysis[8]	X																
Coagulation[9]	X																
Pregnancy test[10]	X	X					X							X	X		

	Screening	Induction					Consolidation Cytarabine and/or post remission HSCT[17]							Following Consolid-ation(s)[36]: up to 2 years post randomization	Post Treatment		
		Induction 1 and Induction 2					Cytarabine[16] 1-4 Cycles (28-day cycle)				HSCT period[34,37]			28-day cycle			
Protocol Activity	**≤28 days prior to study entry**	**Day 1**	**Every 7 days (±2 days)**	**Every 28 days** (±2 days)	**Post first Induc-tion**	**Remis-sion Assess-ment**	**Day 1**	**Day 5**	**Day 10 (±1 days)**	**Day 21** (±7 days)	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**Day 1 (±2 days)**	**End of Treatment Visit[29]** (Within 14 days after last dose)	**Post Treat_ment Follow-Up Visits (±7 days)[30]**	**Long- Term Follow-Up Activity Log (±14 days)[31]**
Triplicate 12 – lead ECG[11]	X	X					X		X					X	X		
ECHO or 2-D MUGA[12]	X																
ANC engraftment[35]														X			
Registration and Treatment[13]																	
Glasdegib or Placebo[14,37]		Oral Once Daily Continuous Dosing. If post remission HSCT[37] interrupt glasdegib/placebo at least 28 days prior to HSCT; may resume following ANC engraftment.															
Daunorubicin Dosing[15]		Days 1-3															
Cytarabine Dosing[16]		Days 1-7					Days 1,3 and 5										
Drug Compliance[18]		Continuous					Continuous							Continuous			
Disease Assessments																	
Bone Marrow Aspirate/ Biopsy[19,30]	X-See[19]				X-See[19]	X-See[19]				X-See[19]				X-See[19,30]		X-See[19,30]	
Bone marrow genetics[20,30]	X				X-See[20]	X-See[20]				X-See[20]				X-See[20]		X-See[20]	
Response Assessment[4]						X				X-See[19]				X-See[19]		X-See[19]	

	Screening	Induction					Consolidation Cytarabine and/or post remission HSCT[17]							Following Consolid-ation(s)[36]: up to 2 years post randomization	Post Treatment		
		Induction 1 and Induction 2					Cytarabine[16] 1-4 Cycles (28-day cycle)				HSCT period[34,37]			28-day cycle			
Protocol Activity	**≤28 days prior to study entry**	**Day 1**	**Every 7 days (±2 days)**	**Every 28 days** (±2 days)	**Post first Induc-tion**	**Remis-sion Assess-ment**	**Day 1**	**Day 5**	**Day 10 (±1 days)**	**Day 21** (±7 days)	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**Day 1 (±2 days)**	**End of Treatment Visit[29]** (Within 14 days after last dose)	**Post Treat_ment Follow-Up Visits (±7 days)[30]**	**Long- Term Follow-Up Activity Log (±14 days)[31]**
Other Clinical Assessments																	
SAE and A E Monitoring[21,34,36]	X	Continuous Monitoring; See[34,36] for HSCT period													X	X[21]	X[21]
Review Prior/ Concomitant Medications and Treatments[22,34]	X	Continuous Collection; except during HSCT period[34]													X		
Recording of red cell and platelet transfusions[23]		Continuous Collection; except during HSCT period[34]													X		
Patient Reported Outcomes[24,30,31,32,]		X	X			X	X	X	X	X	X[32]	X[32]	X[32]	X	X	X	X
Pharmacokinetic Sampling																	
Blood samples for glasdegib Pharmacokinetics (PK)[25]		Refer to Table 2 Pharmacokinetics & ECG Schedule for Patients Receiving Intensive Chemotherapy: Glasdegib/Placebo + /Cytarabine/Daunorubicin															

	Screening	Induction					Consolidation Cytarabine and/or post remission HSCT[17]							Following Consolid-ation(s)[36]: up to 2 years post randomization	Post Treatment		
		Induction 1 and Induction 2					Cytarabine[16] 1-4 Cycles (28-day cycle)				HSCT period[34,37]			28-day cycle			
Protocol Activity	**≤28 days prior to study entry**	**Day 1**	**Every 7 days (±2 days)**	**Every 28 days** (±2 days)	**Post first Induc-tion**	**Remis-sion Assess-ment**	**Day 1**	**Day 5**	**Day 10 (±1 days)**	**Day 21** (±7 days)	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**Day 1 (±2 days)**	**End of Treatment Visit[29]** (Within 14 days after last dose)	**Post Treat_ment Follow-Up Visits (±7 days)[30]**	**Long- Term Follow-Up Activity Log (±14 days)[31]**
CCI [redacted]																	

	Screening	Induction					Consolidation Cytarabine and/or post remission HSCT[17]							Following Consolid-ation(s)[36]: up to 2 years post randomization	Post Treatment		
		Induction 1 and Induction 2					Cytarabine[16] 1-4 Cycles (28-day cycle)				HSCT period[34,37]			28-day cycle			
Protocol Activity	**≤28 days prior to study entry**	**Day 1**	**Every 7 days (±2 days)**	**Every 28 days** (±2 days)	**Post first Induc-tion**	**Remis-sion Assess-ment**	**Day 1**	**Day 5**	**Day 10 (±1 days)**	**Day 21** (±7 days)	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**Day 1 (±2 days)**	**End of Treatment Visit[29]** (Within 14 days after last dose)	**Post Treat_ment Follow-Up Visits (±7 days)[30]**	**Long- Term Follow-Up Activity Log (±14 days)[31]**
Follow Up Assessments																	
Disease progression post treatment[30,31]																X	X
New Anti-cancer therapies since discontinuation of study treatment[30,31]																X	X
Survival Follow-Up Telephone contact[31]																	X

* Patients may continue on treatment for up to a maximum of 2 years as long as they demonstrate clinical benefit.
Abbreviations: **ANC**: absolute neutrophil count; **ECG**: electrocardiogram; **ECHO**: Echocardiogram; **ECOG**: Eastern Cooperative Oncology Group; **HSCT**: hematopoietic stem cell transplant; **MRD**: minimum residual disease; **MUGA**: multigated acquisition scan; **PGIC**: Patient Global Impression of Change; **PK**: pharmacokinetics; **SoA**: Schedule of Activities.

1. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure. Assessments performed as standard of care within 28 days of randomization do not need to be repeated.
2. **Medical History**: Includes cancer history and prior illnesses, and concomitant illnesses.
3. **ECOG Performance Status**: Appendix 3.

4. **Disease Classification and Response Assessment:** AML classified according to 2016 WHO disease classification in Appendix 2. Prognostic genetic risk classification (Appendix 14) and Response Assessments will be done according to 2017 European Leukemia Net (ELN) criteria in Appendix 4. Response assessment includes assessment of EMD (eg disease in CSF).
5. **Physical Examination**: Examination of major body systems, body weight, height, and vital signs (blood pressure and heart rate to be recorded in sitting position). Weight must be recorded at Screening and Day 1 of Induction(s). Height need not be recorded after the first measurement at screening.
6. **Hematology:** No need to repeat on Induction 1 Day 1 if screening assessment is performed within 3 days prior to randomization. The list of required laboratory tests is provided in the protocol (Table 12). If weekly hematology is on same day as another hematology assessment (ie, post first induction, remission, etc), only one hematology sample may be taken on same day. If Induction(s) are extended, hematology tests should continue every 7 days until the next phase begins.
7. **Blood Chemistry:** No need to repeat on Induction 1 Day 1 if screening assessment performed within 3 days prior to randomization. The list of required laboratory tests is provided in the protocol (Table 12). If a weekly chemistry is on same day as another chemistry assessment (ie, post first induction, remission, etc), only one chemistry sample may be taken on same day. If Induction(s) are extended, blood chemistry tests should continue every 7 days until the next phase begins.
8. **Urinalysis:** Should be performed after Screening if clinically indicated. The list of required laboratory tests is provided in the protocol in Table 12.
9. **Coagulation:** Should be performed after Screening if clinically indicated. The list of required laboratory tests is provided in the protocol Table 12.
10. **Pregnancy Tests**: Pregnancy tests (serum/urine) for patients of child-bearing potential only must be performed on two occasions prior to starting study therapy (once at the start of screening and once at the baseline visit, immediately prior to initiation of treatment (first dose), start of every Induction (1,2) during the active treatment period, and at Day 1 of each Consolidation Cycle with single-agent cytarabine, Day 1 of each cycle for single-agent glasdegib/placebo following Consolidation up to 2 years post randomization, and the End of Treatment. Following a negative pregnancy result at screening, appropriate contraception (will be defined in the protocol) must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. It may also be repeated as per request of IRB/ECs (or if required by local regulations), if one menstrual cycle is missed or when potential pregnancy is otherwise suspected during the active treatment period or as clinically indicated.
11. **ECGs (local):** See Table 2 for detailed ECG Schedule.
12. **Echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA)**: Should be repeated before Induction 2 if signs of cardiac toxicity are observed and as clinically indicated thereafter. See Section 7.1.1.
13. **Subject Registration:** Subject registration and assignment of treatment will be obtained from the centralized Interactive Response Technology (IRT).
14. **Glasdegib or Placebo Dosing:** Treatment will be administered in 28-day cycles. Glasdegib or placebo will be administered orally once daily, continuously, preferably in the morning at approximately the same time each day. Where possible, glasdegib will be administered together with daunorubicin IV injection during induction. Patients may continue on glasdegib treatment for up to a maximum of 2 years, as long as they demonstrate clinical benefit and do not have CR MRD-negative disease post consolidation/HSCT as confirmed at 2 consecutive time points.
15. **Daunorubicin Dosing (Induction Only):** Daunorubicin will be given at a dose of 60 mg/m^2 daily as an IV in combination with cytarabine and glasdegib or placebo, on Days 1-3. Induction chemotherapy may be repeated for one additional induction if an unsatisfactory clinical response is observed and there are no signs of cardiac toxicity. If a second induction is needed, Investigators may choose either daunorubicin 60 mg/m^2 IV on Days 1-2 or daunorubicin 60 mg/m^2 IV on Days 1-3 with cytarabine and glasdegib or placebo. If clinical signs of cardiac dysfunction are observed, a repeat MUGA/ECHO should be performed, and must demonstrate a LVEF ≥45% to receive a second course of induction chemotherapy. If a second induction therapy is required, dose must be recalculated if the weight changes by >10%.

16. **Cytarabine Dosing:** Separate cytarabine dosing and schedules will be used for Induction and Consolidation and administered using local package inserts (or SPC) or Investigational Product Manual. Alternative single-agent cytarabine consolidation schedules may be used per local prescribing information.
Induction: Cytarabine will be administered (in parallel to daunorubicin) at a dose of 100 mg/m^2 daily by continuous IV infusion for 7 days on Days 1-7 of induction 1. For the second induction therapy, Investigators may choose either cytarabine 100 mg/m^2 IV on Days 1-5 or on Days 1-7. Dose must be recalculated if the weight changes by >10%.
Consolidation with Cytarabine: Single agent cytarabine will be administered at a dose of 3 g/m^2 IV for adults <60 years and 1- g/m^2 for adults ≥60 years infused over 3 hours, given approximately Q12 hours (morning and evening) on Days 1, 3 and 5 or per local SOC. Alternative single-agent cytarabine consolidation schedules may be used per local prescribing information. Consolidation cytarabine will be repeated every 28 days for up to 4 cycles unless the patient relapses, unacceptable toxicity or patient withdrawal. Dose must be recalculated if the weight changes by >10%. The start of subsequent consolidation cycles may be delayed from the end of the previous cycle to allow for recovery from reversible hematologic or non-hematologic drug-related toxicities. If the consolidation cycle(s) extends longer than 28 days, dosing with glasdegib or placebo should continue daily in the absence of glasdegib-related toxicity that would prevent dosing.
17. **Post remission HSCT:** Follow local and institutional standard of care practices for HSCT conditioning and transplant (see footnote 37).
18. **Drug Compliance**: Dates of all missed doses must be recorded. All glasdegib or placebo bottles including any unused tablets and patient dosing diaries will be returned to the clinic for compliance assessment and drug accountability.
19. **Bone Marrow Assessments for Disease Evaluation.**

    Baseline Bone Marrow Sample: For all patients, a bone marrow **aspirate** sample is **required** at screening plus a bone marrow **biopsy** is **preferred**. Samples taken prior to consent but within 28-days of first dose can be used for disease classification only and need not be repeated. Bone marrow samples required for other study assessments must be done after consent is signed. CCI [redacted]

    Response assessments require bone marrow aspirates and bone marrow biopsies are preferred. All samples for disease assessments will be evaluated by a local laboratory. In case of an inadequate aspirate (eg dry tap), a bone marrow biopsy is required.

    Post-Baseline Time points for Bone Marrow Sampling:

    No bone marrow assessments are necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation or radiological/clinical assessment. For instances when bone marrow assessments are done, bone marrow aspirates are required and bone marrow biopsies are preferred. In cases of an inadequate aspirate (eg dry tap), a bone marrow biopsy is required.

    - **Induction:** Bone marrow assessments will be collected post Induction to determine if a 2nd Induction is needed and at the end of the Remission period to confirm remission status.
    - **Consolidation (applies to Cytarabine and post remission HSCT):** Bone marrow assessments will be collected at the end of the Consolidation period with cytarabine to confirm disease status and determine response. A bone marrow assessment must be done prior to HSCT (may be same marrow assessment as remission assessment or post consolidation assessment).
    - **Glasdegib Therapy following Cytarabine Consolidation or post remission HSCT, up to 2 years**: A bone marrow sample should be obtained at least every 3 months or sooner if relapse is suspected unless other clinical signs of relapse are present and in the clinical judgement of the Investigator aspirate collection is inappropriate.

    Please see Footnote 30 for details on the timing for collection of bone marrow assessments during the Post-Treatment Follow Up period visits.

If an on-treatment BM assessment is scheduled within 3 weeks from the last dose of G-CSF or GM-CSF growth factor, it should be considered "Not Evaluable" for response assessment and a BM evaluation should be repeated at least 3 weeks from the last dose of growth factor.

20. **Bone Marrow genetics:** Genetics (local) will be conducted on all patients using any scheduled or unscheduled bone marrow samples collected during study participation. Please see Footnotes 19 and 30 for details on bone marrow samples collection schedule. Baseline genetics classification must be completed within 28 days of first dose. Since known baseline genetics classification will be used for stratification, investigators must review the available results and stratify subjects into this study. Patients will be stratified according to their 2017 ELN risk category at randomization by the Investigator (Appendix 14). Post baseline genetic assessments may be limited to the abnormalities identified at baseline.
21. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the NCI CTC AE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later. AEs must be collected up until the start of another anticancer therapy if the start of anticancer therapy is earlier than 28 days. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, (ie, prior to undergoing any study related procedure and/or receiving investigational product), through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.
22. **Concomitant Medications and Treatments:** All concomitant medications and treatments should be recorded in the CRF. However, for post remission HSCT period, no concomitant medications will be recorded during the HSCT period.
23. **Red Blood Cells and Platelets Transfusion Recording**: All red blood cell and platelet transfusions, including date of each transfusion and number of red blood cell and platelet units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded.
24. **PRO surveys (MDASI-AML/MDS, EQ 5D 5L, PGIC, PGIS, CCI refer to Section 7.4):** The surveys will be completed by the patient as described in the Schedule of Activities for Induction, Consolidation, and Follow-up (footnotes 30, 31). Interviewer administration may be used under special ccircumstances (eg, subject is visually impaired, forgot their glasses, feels too ill). PROs are collected every 7 days up to 28 days during Induction. There is no PGIC on Day 1 of Induction 1 but it will be administered for Day 1 of Induction 2. See footnote #32 for schedule during HSCT consolidation. CCI [redacted]. Each PRO will continue to be completed at each Post Treatment Follow Up visit and during the Long-Term Follow-up phase by phone. PROs should never be completed more than once on any calendar day. For subjects hospitalized or with a timepoint falling on weekend or holiday, the PRO may be performed on the next business day. If Consolidation(s) are extended PRO will not continue beyond Day 28.
25. **Blood Samples for glasdegib PK**: See detailed information in Table 2 for specific time points.

CCI [redacted]

CCI [redacted]

CCI [redacted]

29. **End of Treatment**: Obtain these assessments if not completed in the last week (last 3 months for BM assessments, unless the patient is coming off study treatment for disease progression). Occurs within 14 days of last dose but may be longer only if dosing was interrupted due to an AE and it led to permanent discontinuation. Subjects continuing to experience toxicity following discontinuation of treatment will be followed at least every 4 weeks by the investigator until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
30. **Post Treatment Follow Up Visits** (First 2 years): A follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product (Section 6.4). Subjects will return to site for visits every 3 months starting from the last dose of study medication, for the first 2 years only. During these visits, physical examinations will be performed, hematology samples and information on any new anti-cancer therapies initiated will be collected, PRO data will be collected, and bone marrow biopsy and/or aspirate samples will be obtained once yearly only from subjects considered to be in clinical remission. Date of post-treatment disease progression recorded in the source notes will be collected.
31. **Long Term Follow up** activity log (Years ≥3): Survival Follow-Up Telephone contact, New Anti-cancer therapies since discontinuation of study treatment, Disease progression, and PRO: Patients will be contacted by telephone every 3 months starting from the last Post Treatment Follow visit to confirm survival status and collect information on any new anti-cancer therapies initiated. Date of post-treatment hematologic relapse or disease progression recorded in the source notes will be collected. During this period, PRO data collection is required and may be collected by phone with data entered by the caller into a Site Tablet. Subjects will be followed up for survival for up to 5 years from the date of randomization of the last patient randomized in the study, or until death, or consent withdrawal. See Section 6.4. Public records may be used to find current contact information and/or to document date of death, if permitted by local law.
32. **PRO Collection during HSCT Post Remission Period (HSCT Period):** PRO will be completed on the day of conditioning regimen administration as described in Section 7.4, then on the day of stem cell infusion prior to infusion and any other clinical activities, then once a month after HSCT infusion (Day 0) until the subject-resumes glasdegib or placebo; then begin PRO assessments on Day 1 in SoA column labeled "Following Consolidation until up to 2 years post randomization). Optimally, subjects will complete electronic PROs (in tablet) themselves. However, if PRO tablets are not available to the subject during this HSCT period, subject if able, will complete the PRO over the phone with a study coordinator so the coordinator may complete the electronic tablet. The study coordinator will make no attempt to clarify, explain, interpret, influence or filter, but simply reading the questions verbatim and transcribing patient choice of answers directly onto the site tablet.

CCI [redacted]

34. **HSCT- related information:** Donor details, type of transplant, day of donor stem cell infusion, and conditioning regimen (including radiation) will be collected in the CRF. Presence of GVHD prior to resuming glasdegib/placebo post HSCT will be reported in the CRF. HSCT–related information must be made available to the B1371019 study and must be able to be monitored. Post Remission HSCT period (**HSCT period**) is defined as time from start of conditioning until resuming glasdegib/placebo, death, withdrawal of consent, or entering follow up period post HSCT. No concomitant medications (including transfusions) will be collected during the HSCT period. Day 0 is defined as the day of stem cell infusion (HSCT). See Section 7.1.8.
35. **ANC engraftment:** ANC engraftment is defined as $\geq 0.5 \times 10^9$/L for 3 consecutive days without growth factor support. ANC engraftment must be documented prior to continuing glasdegib or placebo post-HSCT.

36. **SAE Collection post remission HSCT Period from HSCT (Day 0) until resumption of study therapy, death, or withdrawal:** All deaths regardless of causality, Grade 3 and Grade 4 treatment-related AEs, and SAE events that the investigator believes have at least a reasonable possibility of being related to study drug during the HSCT period are to be reported to the sponsor. Once subjects resume glasdegib or placebo following HSCT, events summarized in Table 13 will be reported.
37. **Interrupt glasdegib/placebo at least 28 days prior to day of hematopoietic stem cell infusion (HSCT).** Following HSCT, subjects may continue glasdegib or matching placebo 30-60 days post first day of HSCT, once there is ANC engraftment, no ≥Grade 2 ongoing GVHD, and no ongoing SAEs that prevent resuming glasdegib or placebo, in the judgement of the investigator.

CCI [redacted]

Table 2. Pharmacokinetics & ECG Schedule for Patients Receiving Intensive Chemotherapy: Glasdegib/Placebo + Daunorubicin/Cytarabine

Assessment	**Screening**	**Induction 1, and Induction 2[1] Day 1**			**Induction 1 and Induction 2[1] Day 10 (±1 day)**			**Consolidation[2, 5] Cycles 1-4, Day 1**			**Consolidation[2, 5] Cycles 1-4, Day 10 (±1 day)**			**Glasdegib following chemotherapy Cycle ≥1, Day 1**	**End of Treatment**
HOUR post-dose[3]		**0[3]**	**1**	**4**	**0[3]**	**1**	**4**	**0[3]**	**1**	**4**	**0[3]**	**1**	**4**	1	
Glasdegib/placebo PK Plasma Samples			X	X	X	X	X	X	X	X					
Triplicate 12-lead ECG[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: **ECG**: electrocardiogram; **PK**: pharmacokinetics.

1. **Induction Phase:** Glasdegib/placebo PK samples to be collected ONLY in Induction 1.

2. **Consolidation Phase:** Glasdegib/placebo PK samples to be collected ONLY in Cycles 1 and 2.

3. **Glasdegib/Placebo PK sample collection:** In all instances, "0 hour" represents a pre-dose collection. The PK sample should be collected within 30 minutes prior to dose administration. Patients should be reminded not to take their study drug prior to arriving at the clinic on protocol scheduled visits. All PK time points are in reference to dosing of glasdegib/placebo. There is a 10% window around the nominal timepoints (1 hour timepoint has a ±6 minute window and the 4 hour timepoint has a ±24 minute window).

4. **Triplicate 12-lead ECGs (local):** At each time point, 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. When matched with PK samples, ECGs will be collected: prior to blood sample collection, such that the blood sample is collected at the nominal planned time. All ECG time points are in reference to dosing of glasdegib/placebo. ECGs will be locally read. A 15-min window for each ECG collection is allowed around the nominal ECG time point.

5. **Glasdegib/Placebo sample collection for HSCT Subjects:** For subjects who go to HSCT, PK samples will be collected as per PK schedule until conditioning therapy is initiated. No consolidation PK samples will be collected once HSCT conditioning begins until the subject resumes glasdegib or placebo.

Table 3. Schedule of Activities for Patients Receiving Non-Intensive Chemotherapy: Glasdegib/Placebo + Azacitidine

	Screening	Treatment							Post Treatment		
		Cycle 1 (28 –day cycle) (-3/+3 day time window)			All subsequent cycles (28 –day cycles) (-3/+3 day time window)	HSCT Period[17]			End of Treatment Visit[27]	Post Treatment Follow-Up Visits (±7 days)[28]	Long-Term Follow-Up Activity Log (±14 days)[29]
Protocol Activity	**(≤28 days prior to study entry)**	**Day 1**	**Day 7 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (-3/+28 days)**	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**(Within 14 days after last dose)**		
Informed Consent[1]	**X**										
Medical History[2]	X										
ECOG Performance Status[3]	X	X			X				X		
Disease Classification[4]	X										
Physical Examination[5,28]	X	X			X				X	per footnote[28]	
HSCT-related information[32]						X					
Laboratory Studies											
Hematology[6,28]	X	X	X	X	X				X	X	
Blood Chemistry[7]	X	X	X	X	X				X		
Urinalysis[8]	X										
Coagulation[9]	X										
Pregnancy Test[10]	X	X			X				X		
Triplicate 12 – Lead ECG[11]	X	X		X	X				X		
Registration and Treatment[12]											
Glasdegib or Placebo[13]		Oral Once Daily Continuous Dosing									
Azacitidine[14]		SC injection or IV Days 1-7 (±3 day time window applicable to each dose)[14]									
Drug Compliance[15]		Continuous							X		
Disease Assessments											
Bone Marrow Biopsy and/or aspirate[16,28]	X- See Footnote[16]				X-See Footnote[16]					X[16]	
Bone Marrow genetics[17,28]	X				X-See Footnote[17]					X-See Footnote[17]	
Response Assessment[4]					X-See Footnote[16]					per footnote[16]	

Table 3. Schedule of Activities for Patients Receiving Non-Intensive Chemotherapy: Glasdegib/Placebo + Azacitidine

	Screening	Treatment							Post Treatment		
		Cycle 1 (28 –day cycle) (-3/+3 day time window)			All subsequent cycles (28 –day cycles) (-3/+3 day time window)	HSCT Period[17]			End of Treatment Visit[27]	Post Treatment Follow-Up Visits (±7 days)[28]	Long-Term Follow-Up Activity Log (±14 days)[29]
Protocol Activity	**(≤28 days prior to study entry)**	**Day 1**	**Day 7 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (-3/+28 days)**	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**(Within 14 days after last dose)**		
Other Clinical Assessments											
Serious and non-serious Adverse Event Monitoring[19]	X	Continuous monitoring; except during HSCT period							X[19]	X[19]	X[19]
Review Prior/Concomitant Treatments[20]	X	Continuous Monitoring; except during HSCT period							X		
Recording of Red Blood Cell and Platelet Transfusions[21]	X	Continuous Monitoring except during HSCT period							X		
Patient Reported Outomes[22,28,29,36]		X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Sampling											
Blood samples for Glasdegib PK[23]	Refer to Table 4 Pharmacokinetics & ECG Schedule for Patients Receiving Non-Intensive Chemotherapy: Glasdegib/Placebo + Azacitidine										
CCI	[redacted]										

Table 3. Schedule of Activities for Patients Receiving Non-Intensive Chemotherapy: Glasdegib/Placebo + Azacitidine

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Protocol Activity	**(≤28 days prior to study entry)**	**Day 1**	**Day 7 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (-3/+28 days)**	**First day of condition-ing**	**HSCT Day 0**	**> Day 0, monthly (±2 days)**	**(Within 14 days after last dose)**		
CCI											
Follow Up Assessments											
Disease progression post treatment[28,29]										X	X
New anti-cancer therapies since discontinuation of study treatment[28,29]										X	X
Survival Follow-Up Telephone contact[29]											X

Abbreviations: **ANC**: absolute neutrophil count; **BM**: Bone Marrow; **C#D#**: Cycle # Day #; **CSF**: cerebrospinal fluid; **ECG**: electrocardiogram; **ECOG**: Eastern Cooperative Oncology Group; **EMD**: Extra Medulary Disease; **GVHD**: Graft versus Host Diease; **HSCT**: hematopoietic stem cell transplant; **MRD**: minimum residual disease; **PK**: pharmacokinetics **WHO:** World Health Organization**.**

1. **Informed Consent:** Must be obtained prior to undergoing any study procedure. Assessments performed as standard of care within 28 days of randomization do not need to be repeated.
2. **Medical History**: Includes cancer history, and prior illnesses, and concomitant illnesses.
3. **ECOG Performance Status**: Appendix 3.
4. **Disease Classification and Response Assessment:** AML classification according to 2016 WHO classification, Appendix 2. Prognostic genetic risk classification (Appendix 14) and Response Assessments according to 2017 European Leukemia Net (ELN) criteria in Appendix 4. Response assessment includes assessment of EMD (eg disease in CSF).
5. **Physical Examination**: Examination of major body systems, body weight, height, and vital signs (blood pressure and heart rate to be recorded in sitting position). Weight must be recorded at Screening and Day 1 of each cycle. Height need not be recorded after the first measurement at screening.
6. **Hematology:** No need to repeat on C1D1 if screening assessment performed within 3 days prior to randomization. The list of required laboratory tests is provided in the protocol (Table 12).
7. **Blood Chemistry:** No need to repeat on C1D1 if screening assessment performed within 3 days prior randomization. The list of required laboratory tests is provided in the protocol (Table 12).

8. **Urinalysis:** Should be performed after Screening if clinically indicated. The list of required laboratory tests is provided in the protocol in Table 12.
9. **Coagulation:** Should be performed after Screening if clinically indicated. The list of required laboratory tests is provided in the protocol.
10. **Pregnancy Tests**: Pregnancy tests (serum/urine) for patients of child-bearing potential only must be performed on two occasions prior to starting study therapy (once at the start of screening and once at the baseline visit, immediately prior to initiation of treatment (first dose), every cycle during the active treatment period and at the End of Treatment. Following a negative pregnancy result at screening, appropriate contraception (will be defined in the protocol) must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. It may also be repeated as per request of IRB/ECs (or if required by local regulations), if one menstrual cycle is missed or when potential pregnancy is otherwise suspected during the active treatment period or as clinically indicated.
11. **ECGs (local):** See Table 4 for detailed ECG Schedule.
12. **Patient Registration:** Patient registration and assignment of treatment will be obtained from the centralized Interactive Response Technology (IRT).
13. **Glasdegib or Matching Placebo Dosing:** Treatment will be administered in 28-day cycles (cycle duration may be extended to allow for toxicity resolution). Glasdegib or placebo will be administered oraly once daily, continuously, preferably in the morning at approximately the same time each day.
14. **Azacitidine dosing:** Treatment can be administered as a SC injection or IV on Days 1-7 (±3 days). Visit time window added to accommodate varying single-agent azacitidine dosing schedules. The start of subsequent cycles can be delayed to allow for toxicity resolution. Post HSCT, there will be no further azacitidine administration.
15. **Drug Compliance**: All glasdegib or placebo bottles including any unused tablets and patient dosing diaries will be returned to the clinic for compliance assessment and drug accountability.
16. **Bone Marrow Assessments for Disease Evaluation**.

    Type of Bone Marrow Sample: **For all patients**, a bone marrow **aspirate** sample is **required** at screening; in addition, a bone marrow **biopsy** is **preferred**. Samples taken prior to consent but within the 28-day window can be used for disease classification only and need not to be repeated. CCI [redacted] Thereafter bone marrow aspirates are required and bone marrow biospsies are preferred for disease evaluation by a local laboratory. Bone marrow aspirates will be required and bone marrow biopsies are preferred during follow up visits. In cases of an inadequate aspirate (eg dry tap), a bone marrow biopsy is required. No bone marrow assessment is necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation or radiological/clinical assessment.

    CCI [redacted]

    Time points for Bone Marrow Sampling:

    - Baseline Bone Marrow must be completed at screening (within 28 days of first dose), Response assessment when CR suspected or after end of Cycle 6; whichever, is earlier. For patients receiving HSCT, a BM aspirate/biopsy must be done prior. Disease assessment will occur when progressive disease (PD) is suspected; then when the investigator suspects progression.
    - Please see Footnote 28 for details on collection of bone marrow assessments during the Post-Treatment Follow Up period.
17. **Post remission HSCT:** Follow local and institutional standard of care practices for HSCT conditioning and transplant. HSCT may occur at any time during study treatment, after a confirmed response (See footnote 35).

18. **Bone Marrow genetics:** Genetics (local) will be conducted on all patients using any scheduled or unscheduled bone marrow samples collected during study participation. Please see Footnotes 16 and 28 for details on bone marrow samples collection schedule. Baseline genetics classification must be completed within 28 days of first dose. Since known baseline genetics classification will be used for stratification, investigators must review the available genetics results and stratify subjects into this study. Patients will be stratified according to their genetic risk category at randomization.
19. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later. AEs must be collected up until the start of another anticancer therapy if the start of anticancer therapy is earlier than 28 days. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, (ie, prior to undergoing any study related procedure and/or receiving investigational product), through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.
20. **Concomitant Medications and Treatments**: All concomitant medications and treatments should be recorded in the CRF.
21. **Red Blood Cells and Platelets Transfusion Recording**: Transfusion history up to 8 weeks prior to randomization should be recorded. All red blood cell and platelet transfusions, including date of **each** transfusion and number of red blood cell and platelet units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded.
22. **PRO surveys (MDASI AML/MDS, PGIS, PGIC, EQ 5D 5L, CCI [redacted] refer to Section 7.4):** The surveys will be by the patient on Day 1 (except there is no PGIC on Day 1 of initial treatment dose – C1D1), 7, 15 of Cycle 1, then Day 1 of each subsequent cycle and at the EOT visit. CCI [redacted]. See Footnote 28, 29 below for details on PRO data collection during the follow up activity period.
23. **Blood samples for Glasdegib PK**: See detailed information in (Table 4) for specific time points.

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27. **End of Treatment:** Obtain these assessments if not completed in the last week (last 3 months for BM assessments, unless the patient is coming off study treatment for disease progression). Occurs within 14 days of last dose but may be longer only if dosing was interrupted due to an AE and it led to permanent discontinuation. Subjects continuing to experience toxicity following discontinuation of treatment will be followed at least every 4 weeks by the investigator until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
28. **Post Treatment Follow Up Visits (First 2 years): Physical Exams, Hematology samples, Yearly Bone Marrow samples for patients in remission, Anti-cancer therapies since discontinuation of study treatment, Disease progression post-treatment, and PRO:** A follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product (Section 6.4). Patients will return to site for visits every 3 months starting from the last dose of study medication, for the first 2 years only. During these visits, physical examinations will be performed, hematology samples and information on any new anti-cancer therapies initiated will be collected, PRO data will be collected, and bone marrow assessment samples will be obtained once yearly only from patients in remission. Date of post-treatment disease progression recorded in the source notes will be collected.
29. **Long Term Follow up activity log (Years ≥3): Survival Follow-Up Telephone contact, New Anti-cancer therapies since discontinuation of study treatment, Disease progression, and PRO:** Patients will be contacted by telephone every 3 months starting from the last Post Treatment Follow visit to confirm survival status and collect information on any new anti-cancer therapies initiated. Date of post-treatment hematologic relapse or disease progression recorded in the source notes will be collected. During this period, PRO data collection is required and may be collected by phone with data entered by the caller into a Site Tablet. Patients will be followed up for survival for up to 5 years from the date of randomization of the last patient randomized in the study, or until death, or consent withdrawal. Public records may be used to find current contact information and/or to document date of death, if permitted by local law.

CCI [redacted]

32. **HSCT related information**: Donor details, type of transplant, day of donor stem cell infusion, and conditioning regimen (including radiation) will be collected in the CRF. Presence of GVHD prior to resuming glasdegib/placebo post HSCT will be reported in the CRF. HSCT–related information must be made available to the B1371019 study and must be able to be monitored. Post Remission HSCT period (HSCT period) is defined as time from start of conditioning until resuming glasdegib/placebo, death, withdrawal of consent, or entering follow up period post HSCT. No concomitant medications (including transfusions) will be collected during the HSCT period. Day 0 is defined as the day of stem cell infusion (HSCT). See Section 7.1.8.
33. **ANC engraftment**: ANC engraftment is defined as $\geq 0.5 \times 10^9$/L for 3 consecutive days without growth factor support. ANC engraftment must be documented prior to continuing glasdegib or placebo post HSCT.
34. **SAE Collection post remission** HSCT Period from HSCT (Day 0) until resumption of study therapy, death, or withdrawal: All deaths regardless of causality, Grade 3 and Grade 4 treatment related AEs, and SAE events that the investigator believes have at least a reasonable possibility of being related to study drug during the HSCT period are to be reported to the sponsor. Once subjects resume glasdegib or placebo following HSCT, events summarized in Table 13 will be reported.

35. **Interrupt glasdegib/placebo at least 28 days prior to day of hematopoietic stem cell infusion (HSC**T). Following HSCT, subjects may continue glasdegib or matching placebo 30 -60 days post first day of HSCT, once there is ANC engraftment, no ongoing ≥ Grade 2 GVHD, and no ongoing SAEs that prevent resuming glasdegib or placebo, in the judgement of the investigator. Patients may continue on glasdegib treatment following HSCT or up to 2 years post randomization or until CR MRD-negative disease is confirmed at 2 consecutive time points post HSCT, whichever comes first. The 2 consecutive time points will be done as part of the scheduled marrow assessments.
36. **PRO Collection during HSCT** Post Remission Period (HSCT Period): PRO will be completed on the day of conditioning regimen administration prior to dosing and any other clinical activities, then on the day of stem cell infusion prior to infusion and any other clinical activities, then once a month after HSCT infusion (Day 0) until the subject resumes glasdegib or placebo; then begin PRO assessments on Day 1 in SoA column labeled "Following Consolidation until up to 2 years post randomization". Optimally, subjects will complete electronic PROs (in tablet) themselves. However, if PRO tablets are not available to the subject during this HSCT period, subject if able, will complete the PRO over the phone with a study coordinator so the coordinator may complete the electronic tablet. The study coordinator will make no attempt to clarify, explain, interpret, influence or filter, but simply reading the questions verbatim and transcribing patient choice of answers directly onto the site tablet.

Table 4. Pharmacokinetics & ECG Schedule for Patients Receiving Non Intensive Chemotherapy: Glasdegib/Placebo + Azacitidine

Assessment	**Screening**	**Cycle 1, Day 1**			**Cycle 1, Day 15** (±3 days)			**Cycle 2-3, Day 1**[3] (-3/+28 days)			**Cycles ≥4, Day 1** (-3/+28 days)	**End of treatment**
HOUR post-dose[1]		0[1]	**1**	**4**	0[1]	**1**	**4**	0[1]	**1**	**4**	**1**	
Glasdegib/placebo PK Plasma Samples			X	X	X	X	X	X	X	X		
Triplicate 12-lead ECG[2]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: **ECG**: electrocardiogram; **PK**: pharmacokinetics

1. **Glasdegib/Placebo PK Sample Collection:** In all instances, "0 hour" represents a pre-dose collection. The PK sample should be collected within 30 minutes prior to dose administration. Patients should be reminded not to take their study drug prior to arriving at the clinic on protocol scheduled visits. All PK time points are in reference to dosing of glasdegib/placebo. There is a 10% window around the nominal timepoint, (1 hour timepoint has a ±6 minute window and the 4 hour timepoint has a ±24 minute window).

2. **Triplicate 12-Lead ECGs:** At each time point, 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. When matched with PK samples, ECGs will be collected: prior to blood sample collection, such that the blood sample is collected at the nominal planned time. All ECG time points are in reference to dosing of glasdegib/placebo. ECGs will be locally read. A 15-min window for each ECG collection is allowed around the nominal ECG time point.

3. **PK samples** to be collected only on Cycle 2 Day 1.

1. INTRODUCTION

1.1. Indication

Glasdegib is being studied in combination with azacitidine for the treatment of adult patients with previously untreated acute myeloid leukemia who are not candidates for intensive induction chemotherapy (Non-intensive AML population).

Glasdegib is being studied in combination with cytarabine and daunorubicin for the treatment of adult patients with previously untreated acute myeloid leukemia (Intensive AML population).

1.2. Background

1.2.1. Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is a heterogeneous cancer of the hematopoietic system characterized by increased blast counts, pancytopenias causing infections and bleeding, and reduced survival. AML is a genetically heterogeneous malignancy characterized by multiple genetic mutations at the time of diagnosis that evolve with treatment, resulting in treatment resistance, disease relapse, and reduced survival. It is estimated that there will be 21,380 new cases and 10,590 deaths from AML in the United States in 2017.[7] Incidence rates in Europe are similar to rates in the United States.[8] AML is a disease of older people and is uncommon before the age of 45. The average age of a patient with AML is about 67 years.

Existing standards of care, such as anthracycline + cytarabine or hypomethylating agents like decitabine and azacitidine, can induce complete remissions in 5-70% of patients; however, remissions are not durable and disease relapse occurs in up to 60% of patients.[9] For AML patients unable to receive intensive chemotherapy, existing standard treatments like low-dose cytarabine (LDAC) are associated with response rates <20% and median overall survival (mOS) times of 5-6.5 months. Hypomethylating agents, azacitidine and decitabine, although not approved in the United States (US) specifically for AML, have shown improved overall survival (OS) vs LDAC in AML patients not suitable for intensive chemotherapy.

Midostaurin (Rydapt®) is indicated for use in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML who are Fms-like tyrosine kinase 3 (FLT3) mutation-positive.[19] Approval in 2017 was based on the Phase III RATIFY (CALGB 10603 [Alliance]) clinical trial resulting in a 23% reduction in the risk of death compared with chemotherapy alone (hazard ratio [HR] = 0.77, 95% confidence interval [CI], 0.63, 0.95; 2 sided p=0.016)[3].[10] Event-free survival was significantly higher for Rydapt plus chemotherapy versus chemotherapy alone (median of 8.2 months compared to 3.0 months, HR = 0.78, 95% CI 0.66, 0.93 and 2 sided p=0.004).

The most frequent adverse reactions were febrile neutropenia, nausea, vomiting, mucositis, headache, musculoskeletal pain, petechiae, device-related infection, epistaxis, hyperglycemia and upper respiratory tract infections.

Reducing the incidence of disease progression to prolong survival remains the highest unmet medical need in the treatment of AML patients.[11-13]

Glasdegib has shown activity in myelodysplastic syndrome (MDS) and AML with improved response rates and improved OS.

Genetic and functional studies have demonstrated that AML develops as a result of acquisition of genetic and epigenetic alternations that result in abnormal differentiation and unlimited cellular self-renewal. The World Health Organization (WHO) 2016 classification defines AML as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(6;16), inv(160)]. In 2016, the World Health Organization (WHO) revised their classification of myeloid neoplasms and acute leukemia (Appendix 2).[20] In this revision, acute promyelocytic leukemia (APL) with a t(15:17) gene fusion, was renamed as APL with PML-RARA. AML with t(9:22) was renamed AML with BCR-ABL breakpoint cluster region-Abelson 1 (BCR-ABL1) to identify the rare cases that may benefit from tyrosine kinase inhibitor (TKI) therapy.[21,22]

1.2.2. Hedgehog Signaling Pathway and Glasdegib Mechanism

Glasdegib is a selective, orally administered inhibitor of the seven-transmembrane protein, smoothened (SMO), which demonstrates potent and selective inhibition of Hedgehog (Hh) signaling in vitro and significant antitumor efficacy in vivo. The Hh signaling pathway regulates cell differentiation and self-renewal in the developing embryo, and is typically silenced in adult tissues. Aberrant Hh signaling may result from mutations in key pathway genes, non-mutational mechanisms related to the secretion of Hh ligands, or from cells in the tumor microenvironment. Aberrant Hh signaling has been identified in a variety of human leukemia and leukemic stem cells (LSCs).[1] Upregulation of Hh pathway components has been observed in chemo resistant AML cell lines in vitro, and pharmacological inhibition of the Hh pathway resulted in decreased multi-drug resistance 1 (MDR-1) or P-glycoprotein (P-gp) expression in these cells.[4] The SMO inhibitors, vismodegib (Erivedge®)[5] and sonidegib (Odomzo®)[6] have been demonstrated to be safe and effective in the treatment of patients with advanced basal cell carcinoma. Glasdegib is being developed for indications in myeloid malignancies.

In nonclinical models, SMO, acting via its effector, Glioma-associated oncogene homolog 2 (GLI2), has been implicated in the maintenance of LSC dormancy and associated resistance to chemotherapy and targeted therapy, while inhibition of SMO via glasdegib can cause LSCs to re-enter the cell cycle.[22-24] Recrudescence of LSCs is prevented in preclinical hosts that were pre-treated with Hh pathway inhibitors, including glasdegib.[22] Consistent with these effects, glasdegib sensitized AML cells to cytosine arabinoside, and abrogated resistance to cytosine arabinoside in AML cells co-cultured with stromal cells.[22] Thus, Hh pathway inhibitors such as glasdegib may have a role in the treatment of AML patients.

Gene profiling analysis showed that treatment with glasdegib modulates self-renewal and cell-cycling in AML by encouraging quiescent LSCs into cell cycle. NANOG transcript level may be a responsive biomarker during treatment with glasdegib in AML.[25] Upon GLI binding to the NONOG pluripotency promoter, GLI-NANOG axis promotes stemness and growth in several cancers. When NANOG expression was examined in primary AML patient bone marrow samples following treatment with glasdegib, NONOG transcript levels decreased along with GLI-target genes; such as, GLI1 and patched (PTCH). Upregulation of Hh pathway components has been observed in chemo-resistant AML cell lines in vitro, and pharmacological inhibition of the Hh pathway resulted in decreased multi drug resistance (MDR-1) or P-glycoprotein (P-gp) expression in these cells.[4] Additional evidence for the importance of the Hh pathway in leukemia is derived from patients enrolled in the completed single agent hematology trials. Importantly, these preliminary data suggest the mechanism of action of Hh inhibition in leukemia appears to be mobilization of blast cells from the bone marrow to the peripheral blood, with subsequent expansion and differentiation of LSCs.[23]

1.2.3. Glasdegib Nonclinical Toxicology

Details of the nonclinical safety program are provided in the current Investigator's Brochure, Section 5.3.

1.2.4. Clinical Development

In the clinical development program to date, glasdegib has been studied in >300 patients across multiple diseases, and >100 healthy participants.

1.2.4.1. Clinical Pharmacology of Glasdegib

Glasdegib has been orally administered to humans at doses ranging from 5 mg to 640 mg QD. Following daily dosing as a single agent, steady state was usually achieved by Day 8 of treatment. In patients with myeloid malignancies and solid tumors, the time to maximum plasma concentration (T_{max}) typically ranged from 1-4 hours both after a single dose and at steady state.

The geometric mean (geometric %CV) apparent volume of distribution (V_z/F) of glasdegib was 188 (20) L following a single dose of 100 mg glasdegib in patients with hematologic malignancies and exceeded the typical plasma volume (3L) suggesting that glasdegib is distributed into tissues from plasma. In nonclinical studies, the fraction unbound in human plasma (fu) was 0.0899 at a concentration of 10 µM (3744 ng/mL). The absolute bioavailability of glasdegib was 77.12%.

In the first-in-participant (FIP) study (B1371001), following peak plasma concentrations obtained after oral administration, glasdegib plasma concentrations appear to have a biexponential decline. Glasdegib accumulated following repeated dosing with a median accumulation ratio (R_{ac}) ranging from 1.2 to 2.5. Observed C_{max} and AUC of glasdegib increased in a dose-proportional manner over the dose range of 5 mg to 600 mg QD after single and multiple dosing.

CYP3A4 is the enzyme primarily responsible for the metabolism of glasdegib, with minor contributions from other pathways. Renal excretion of unchanged glasdegib is ~17% of the total administered dose (100 mg).

To estimate the impact of a inhibition of CY3A4/5 on glasdegib plasma exposures, an interaction study with ketoconazole, a strong CYP3A4/5 inhibitor, was conducted in 14 healthy volunteers. A single 200-mg oral dose of glasdegib in the presence of ketoconazole compared to 200-mg dose of glasdegib alone resulted in higher glasdegib exposures, with the mean plasma exposure (AUC_{inf}) ratio of 2.4 (90% CI: 2.15, 2.68) and the mean peak plasma concentration (C_{max}) ratio of 1.4 (90% CI: 1.24-1.58).

A second interaction study to estimate the effect of a strong CYP3A4/5 inducer on glasdegib PK was conducted using rifampin, a strong inducer of CYP3A4/5, in 12 healthy volunteers. In the presence of rifampin, there was a 70% decrease (90% CI: 26, 31) in plasma exposures (AUC_{inf}) and a 35% decrease (90% CI: 57,73) in peak plasma concentration (C_{max}) of a single 100 mg oral dose of glasdegib when compared to glasdegib alone indicating that CYP3A4/5 related metabolism is a major pathway for glasdegib biotransformation.

An evaluation of the effect of food on the maleate salt 100 mg tablet formulation (B1371026) showed a reduction in glasdegib C_{max} and AUC_{inf} [geometric mean ratio (90% CI): 76% (65%, 88%) and 86% (81%, 92%) respectively]. Co-administration of glasdegib with a pH altering agent (the proton pump inhibitor, rabeprazole) under fasting conditions, resulted in no change in glasdegib AUC_{inf} (geometric mean ratio [90% CI]: 100.58% [93.19%, 108.55%]) and a 19.5% decrease in glasdegib C_{max} (geometric mean ratio [90% CI]: 80.46% [70.68%, 91.59%]) compared with a single dose of glasdegib administered alone. This impact of PPI on the PK of glasdegib was not considered to be clinically meaningful.

A Phase 1, single-center, randomized, 4-period, 4-sequence, 4-treatment (glasdegib at therapeutic and supratherapeutic exposure and placebo [blinded]; moxifloxacin [open label]), single dose, 4-way crossover thorough QT (TQT) study was conducted that investigated the effect of glasdegib on cardiac repolarization in 36 healthy participants. Absence of a large effect of glasdegib on the QTcF interval was demonstrated at the therapeutic (100 mg QD steady state glasdegib exposures) and supratherapeutic (~2X the steady state glasdegib exposures) doses as the upper bound of the 2-sided 90% CIs for all time-matched least squares mean differences between glasdegib (150 mg and 300 mg) and placebo was below the pre-specified criterion of 20 msec – the threshold of clinical concern in oncology. None of the participants had absolute QTcF interval of ≥480 msec or increase from baseline in QTcF interval ≥30 msec after receiving any treatment.

Additional clinical pharmacology information for this compound may be found in the single reference safety document (SRSD), the Investigator's Brochure.

1.2.4.2. Relevant Clinical Studies with Glasdegib

B1371003 Phase 2 Randomized Non-intensive Chemotherapy

AML + MDS patients not eligible for intensive chemotherapy were randomized 2:1 to glasdegib + LDAC or LDAC alone. The combination of glasdegib 100 mg QD plus LDAC resulted in a clinically meaningful and statistically significant improvement in OS in the AML subgroup that comprised 88% of all randomized participants (hazard ratio (HR)=0.463 [95% confidence interval (CI): 0.299, 0.717], p=0.0002), with an mOS of 8.3 months versus 4.3 months. Improvement in OS was consistent across pre-specified subgroups by good/intermediate and poor cytogenetic risk. The demonstrated benefits in OS were supported by improvements in CR rates, which appeared to be consistent across the clinical trial program when glasdegib was combined with standard-of-care chemotherapy for AML or MDS such as azacitidine, decitabine, or 7+3 in the context of historical controls.

B1371003 Phase 2 Single-Arm Intensive Chemotherapy

In a single-arm open-label trial in AML + MDS patients who were able to receive intensive chemotherapy with 7+3, including approximately 25% with adverse or poor cytogenetic risk disease, there was at least a 1.5-fold increase in mOS in each of the ELN risk stratifications, including adverse risk, as compared to historical controls, which is supportive of the OS benefit seen in the randomized Phase 2 part of Study B1371003. This improvement in OS observed with glasdegib treatment did not appear to be influenced by HSCT given that the OS results with and without censoring for patients who underwent HSCT were similar.

The mOS for 44 AML patients (29 deaths) age >60 yrs is presented in Table 5, in the context of historical control.

Table 5. Median Overall Survival (mOS) in Patients >60 Years Stratified by European Leukemia Net (ELN) Risk Criteria

Risk Group	7+3 (Historical Röllig et al, 2011, N=710) Months	Glasdegib Plus 7+3 (n=44*) Months	Increase in mOS withAddition of Glasdegib (29 deaths)
Favorable	14.6	Not reached (n=9)	Not estimable
Int-1	9.5	15.7 (n=12)	65.3%
Int-2	9.2	13.4 (n=11)	45.7%
Adverse	4.8	8.5 (n=10)	77.1%

*2 pts were not classifiable by ELN risk.

Although the CR rates do not appear to be higher than those reported historically for older AML pts receiving intensive chemotherapy, the mOS stratified by subgroup appears improved by adding glasdegib, as may be expected for an agent that targets LSCs. The combination of glasdegib with '7+3' was well-tolerated, with a safety profile consistent with that in AML patients receiving standard intensive chemotherapy.

B1371012 Phase 1b/2

In Study B1371012, 12 patients with high risk MDS, CMML, or AML were treated with glasdegib 100 mg PO QD in combination with azacitidine 75 mg/m^2 daily for 7 days subcutaneously in a safety lead-in cohort. No evidence of drug-drug interaction (DDI) with azacitidine was noted. As of March 2017, 5 of the 12 participants responded: 3 participants with CR (all AML) and 2 participants with marrow CR.[14]

Updated details of the clinical safety program are provided in the current Investigator's Brochure.

1.3. Rationale for Drug Combinations and Dosing

1.3.1. Rationale for Glasdegib in Combination with Azacitidine as Non-Intensive Chemotherapy

In the randomized cohort of Study B1371003, glasdegib (100 mg PO QD) demonstrated a statistically significant and clinically meaningful improvement in median overall survival (mOS) when combined with LDAC vs LDAC alone in elderly AML patients not suitable for intensive chemotherapy, with no new safety signals identified.

For AML patients who are not expected to tolerate intensive chemotherapy, treatment alternatives are limited to best supportive care, low-intensity treatment, or clinical trials with investigational drugs. When compared with conventional care regimens, azicitidine increased mOS from 6.5 months to 10.4 months.[16] In the European Union (EU), azacitidine (Vidaza®) has been approved for patients aged ≥65 years with AML who are not eligible for HSCT based on data from the AML-001 study.[9] Median OS was 10.4 months. The one year survival rate was 46.5%. Grade 3-4 anemia, neutropenia, febrile neutropenia, and thrombocytopenia rates, respectively, were 16%, 26%, 28%, and 24% with azacitidine. Azacididine is not curative; therefore, continuing glasdegib or placebo until disease progression or toxicity is reasonable.

Preclinical data demonstrated synergistic activity when a SMO inhibitor erismodegib, was combined with 5-azacitidine, a hypomethylating agent.[32] Silencing of chromosomes 5 and 7 enhances the activity of 5-azacitidine. In a 5-azacitidine ribonucleic acid (RNA)-interference sensitizer screen to identify gene targets within the commonly deleted regions of chromosomes 5 and 7, drugs that inhibited SMO (erismodegib and vismodegib) showed single-agent activity in AML cell lines. Combination of erismodegib with 5-azacitidine demonstrated synergistic activity in multiple AML cell lines regardless of the extent of Hh pathway gene expression.

In Study B1371012, serial PK samples were collected for both glasdegib and azacitidine alone and in combination during the first cycle of treatment, to assess for potential drug-drug interaction. The PK parameters for glasdegib and azacitidine were similar when dosed separately or in combination, indicating no evidence of drug-drug interaction potential.

Additional information for glasdegib may be found in the Single Reference Safety Document (SRSD), the Investigator Brochure. For the purposes of this trial, the SRSD for azacitidine is the EU SPC for Vidaza®.[33]

1.3.2. Rationale for Glasdegib in Combination with Daunorubicin and Cytarabine as Intensive Chemotherapy

When combined with glasdegib (100 mg PO QD), improvements in response rates, reductions in disease relapse frequency, and improvements in OS in the context of historical controls have been observed both in different populations (MDS, post-allogeneic stem cell transplant, elderly AML and suitable for intensive chemotherapy) and with different treatment combinations commonly used in the treatment of AML patients (azacitidine, decitabine, '7+3', allogeneic stem cell transplant. AML relapse does not typically occur after 2 years; therefore, it is reasonable to administer glasdegib or placebo up to 2 years post randomization.[12,16]

CR is achieved in 60%-80% of younger adults and 40%-60% adults (age ≥60) following administration with standard intensive '7+3' chemotherapy consisting of 7 days of cytarabine (100-200 mg/m^2) and 3 days of an anthracycline (ie, daunorubicin 45-60 mg/m^2.[12,16] Thus, a '7+3' is a reasonable induction regimen for patients who are medically fit.[34]

The AML14 trial enrolled 1273 patients, predominantly aged >60 years (although younger patients were allowed) with AML and High Risk MDS.[35] The overall response rate across all arms was 62% (CR 54%, CR without platelet/neutrophils recovery 8%); 5-year survival was 12%, and no benefits were observed in either dose escalation schedule. To determine if the addition of a Hh inhibitor can increase intensive chemotherapy response rates, glasdegib will be administered once daily and continuously starting on Day 1, along with the start of cytotoxic therapy. This schedule is consistent with other mobilizing/cytotoxic combination studies, and will allow cells time to transit from the marrow to the peripheral blood compartment.[36]

The most common consolidation regimens include single-agent cytarabine at high doses and multiagent chemotherapy which lead to similar outcomes. High –dose cytarabine (HIDAC; 2000-3000 mg/m^2) is commonly used.[37]

Allogeneic HSCT is generally recommended as a standard of care consolidation therapy, especially in patients who are medically suitable for HSCT and with adverse genetics.[16]

The relapse incidence without the procedure is expected to be 35% to 40%.

In the Phase 1b portion of Study B1371003 for glasdegib in combination with 7+3, the PK of 100 mg QD glasdegib at steady state were in line with expected exposures and the exposures of 7+3 were in line with historically reported exposure data.

Additional information for glasdegib may be found in the SRSD, the Investigator Brochure. For the purposes of this trial, the SRSD is the EU Summary of Product Characteristics (SPC) for cytarabine[38] and daunorubicin.[39]

1.3.3. Rationale for Glasdegib Dosing and Schedule

B1371001 first-in-human study identified the MTD for single-agent glasdegib continuous administration as 400 mg QD, and the RP2D as 200 mg QD in patients with select hematologic malignancies. Study B1371003 with glasdegib in combination with LDAC and intensive chemotherapy (cytarabine/daunorubicin) initially tested both glasdegib 100 mg QD and 200 mg QD starting dose levels in the Phase 1b portion of the study. However the clinical dose of 100 mg QD (MTD-4) was selected as the dose for further evaluation in the Phase 2 portions of the study on the basis of the observed clinical activity, safety and tolerability profile, modulation of hedgehog pathway activity in surrogate tissue, and information relating to the possible impact of a CYP3A4 inhibitor. These data provided a compelling rationale for the 100 mg QD dose of glasdegib being a safe and clinically effective dose in combination with azacitidine or cytarabine/ daunorubicin.

CCI

[redacted]

1.5. Summary of Benefit Risk Assessment

Glasdegib is a selective, once daily oral tablet SMO inhibitor with a safety profile that appears consistent with other approved, marketed SMO inhibitors based upon data reported in the IB (September 2018). In the ongoing clinical development program, glasdegib significantly improved OS in a prospective randomized study in combination with LDAC in AML patients not suitable for intensive chemotherapy.

Data are mature, as median duration of follow-up is longer than mOS.

The safety profile of the addition of glasdegib to LDAC was generally tolerable and manageable. Despite the differences in treatment and follow-up duration between the two arms, increases in cytopenias were not accompanied by significant increases in sepsis or bleeding. The principle SMO inhibitor toxicities of dysgeusia, alopecia, and muscle spasms were mostly Grade 1 or 2 in severity and manageable with continued dosing with or without dose modification.

Improvements in response rates, reductions in disease relapse frequency, and improvements in OS in the context of historical controls have been observed both in different populations (MDS, post-allogeneic stem cell transplant (SCT), and elderly patients with AML suitable for intensive chemotherapy) and with different AML treatment regimens commonly used in the treatment of AML patients (azacitidine, decitabine, '7+3', allogeneic SCT).

The clinical safety database of glasdegib contains over 300 patients with hematologic malignancies who received the glasdegib recommended daily dose of at least 100 mg. The safety profile observed so far appears consistent with that reported for the SMO inhibitor class and the underlying chemotherapy backbones.

Based on the results from B1371003, 2 prospective randomized (1:1), double-blind, placebo-controlled registration trials in patients with newly diagnosed AML are proposed: in the first study, 400 AML patients suitable for intensive chemotherapy will be randomized to receive '7+3'+ glasdegib (Arm A) or '7+3'+ placebo (Arm B). In the second study, 320 AML patients not suitable for intensive chemotherapy per investigator will be randomized to receive azacitidine + glasdegib (Arm A) or azacitidine + placebo (Arm B). The primary endpoint for both trials will be OS. Both studies will be powered, conducted, and analyzed separately and independently under 1 protocol (B1371019) to maximize efficiency. Together, the trials can provide substantial evidence to register glasdegib in AML patients treated in combination with 7+3 or with azacitidine.

2. STUDY OBJECTIVES AND ENDPOINTS

Protocol B1371019 consists of 2 independent studies: an intensive chemotherapy study and non-intensive chemotherapy study. Within each study, subjects will be randomized to chemotherapy with either glasdegib or matching placebo. The primary and secondary endpoints for each study will be analyzed separately. Response criteria for AML are defined by the 2017 ELN recommendations.[16]

The objectives and endpoints for each study are the same unless otherwise specified and are described below:

Primary Objective:	**Primary Endpoint:**
• To demonstrate that glasdegib is superior to placebo in combination with azacitidine (non-intensive study) or cytarabine and daunorubicin (intensive study) in prolonging OS in subjects with untreated AML.	• Overall survival.

Secondary Objectives:	Secondary Endpoints:
• To compare fatigue score post-baseline as measured by MDASI-AML/MDS in both treatment arms; • To compare glasdegib versus placebo in combination with azacitidine (non-intensive study) or '7+3' (cytarabine and daunorubicin) in improving other clinical efficacy measures; • To estimate the duration of response in both treatment arms; • To estimate the time to response in both treatment arms in the Non-intensive study only; • To compare Event-free Survival (EFS) in both treatment arms; • To compare PRO measurements in both treatment arms; • To evaluate the overall safety profile in both treatment arms; • To evaluate laboratory abnormalities in both treatment arms; • To characterize the PK of glasdegib; • To characterize treatment effects on the QTc interval.	• Fatigue score measured by the MDASI-AML/MDS questionnaire; • Rate of CR (including $CR_{MRD\text{-}negative}$ as assessed by multiparametric flow cytometry), CRi as defined by the ELN recommendations (2017), MLFS, PR, and CR with partial hematologic recovery (CRh) for the Non-intensive study only; • Duration of response (defined as CRi or better or CRh or better if applicable):* • Time to response (CRi or better or CRh or better)* in the non-intensive study only; • Event-free Survival; • PROs as measured by the M.D. Anderson Symptom Inventory AML/MDS Module (MDASI-AML/MDS), EuroQoL 5 Dimension questionnaire 5-Level version (EQ-5D-5L), Patient Global Impression of Symptoms (PGIS) and Patient Global Impression of Change (PGIC); • Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; • PK of glasdegib; • QTc interval.
CCI [redacted]	[redacted]
[redacted]	[redacted]

* CRi or better includes CR (including $CR_{MRD\text{-}negative}$) or CRi for intensive chemotherapy subjects, and CR (including $CR_{MRD\text{-}negative}$), CRh, or CRi for non-intensive chemotherapy subjects. CRh or better is only defined for non-intensive chemotherapy subjects as CR (including $CR_{MRD\text{-}negative}$) or CRh.

The Intensive and Non-Intensive Chemotherapy studies will use the same external data monitoring committee (E-DMC).

3. STUDY DESIGN

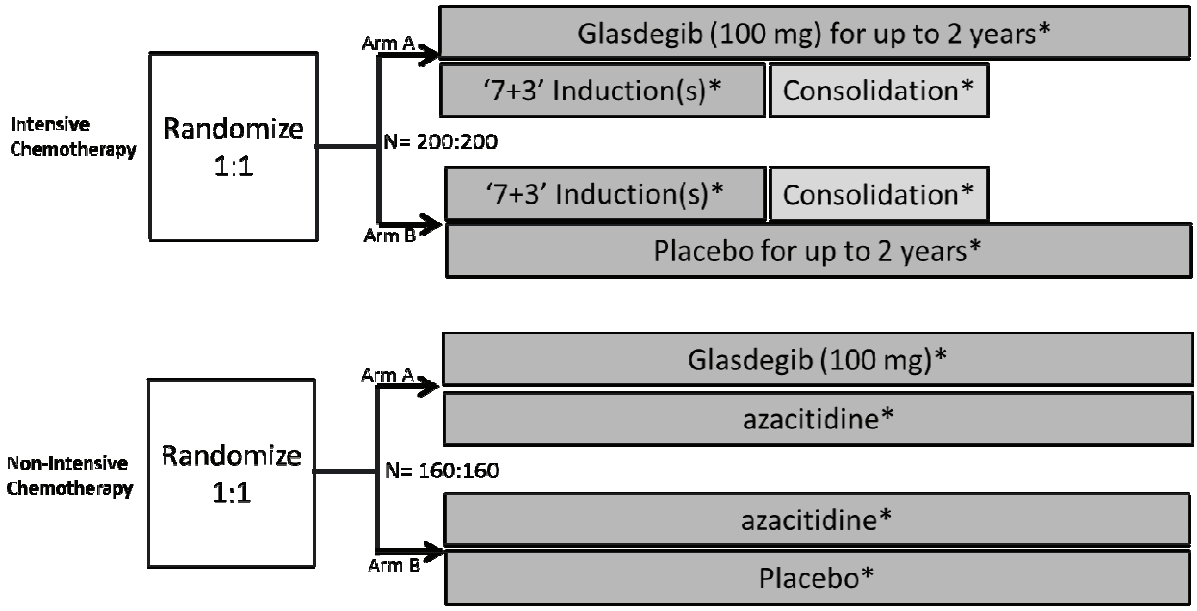
Two separate registration trials conducted under one protocol number are proposed to adequately and independently evaluate the addition of glasdegib in intensive and non-intensive chemotherapy populations. Each study will have an experimental treatment arm and a placebo arm.

Study B1371019 (Figure 1) is a randomized (1:1), double-blind, multi-center, placebo controlled study of chemotherapy in combination with glasdegib versus chemotherapy in combination with placebo in adult patients with previously untreated AML (excluding APL with PML-RARA, AML with BCR-ABL1 and active central nervous system [CNS] leukemia) to support the proposed indication statements:

- Intensive Study: Glasdegib is being studied in combination with cytarabine and daunorubicin for the treatment of adult patients with untreated AML.

- Non-intensive Study: Glasdegib is being studied in combination with azacitidine for the treatment of adult patients with untreated AML who are not candidates for intensive induction chemotherapy.

Figure 1. Schematic of Study Design



* Section 5.5 describes dosing details for the intensive chemotherapy regimen(s) [including '7+3' or '5+2' option for Induction 2], non-intensive chemotherapy regimen, and experimental study drugs.

Assignment to the Intensive Study or the Non-Intensive Study will be made by the Investigator based on the 2017 ELN recommendations.[16]

The treatment arm allocation for Arm A or Arm B within each study will be operated by the sponsor following the rules defined in Section 5.1.

In each study, the primary endpoint will be OS, and the secondary endpoints would include response, duration of response, time to response, EFS, safety, CCI [redacted], PROs, and PK. Study visits would occur on the first day of each cycle during the treatment period, and after end of treatment per the Schedule of Events (Table 1, Table 2 and Table 3, Table 4) to evaluate safety, disease progression, further anti-cancer therapy, or death.

Intensive Chemotherapy Study:

Subjects will be stratified at randomization by genetic risk (favorable vs intermediate vs adverse by ELN genetic risk categories)[16] and age (≤60 years vs >60 years).

A total of 400 subjects eligible to receive intensive chemotherapy per investigator assessment will receive treatment as follows:

- Experimental Therapy: Glasdegib 100 mg PO or matching placebo will be administered by mouth daily beginning on Day 1 and is to continue up to 2 years post randomization. Following consolidation therapy, glasdegib or placebo will be administered daily for up to 2 years after randomization or until they have 2 consecutive CR MRD-negative central laboratory results, whichever comes first. Daily Glasdegib 100 mg PO or matching placebo will continue throughout Induction(s) and Consolidation therapies regardless of dose modifications/delays in the chemotherapy.

    - For HSCT consolidation, glasdegib or placebo will be interrupted at least 28 days before HSCT Day 0 (day of HSCT) and resumed 30-60 days post HSCT, once there is ANC engraftment ($\geq 0.5 \times 10^9$/L for 3 consecutive days without growth factor support), no ongoing ≥ Grade 2 graft-versus-host disease (GVHD), and no ongoing SAEs that prevent resumption of glasdegib or placebo in the judgement of the investigator.

- Induction chemotherapy: '7+3' (cytarabine 100 mg/m^2 IV for 7 days by continuous infusion and daunorubicin 60 mg/m^2 for 3 days). If a second induction is needed, Investigators may choose either a 5 day cytarabine continuous infusion plus daunorubicin for 2 days ('5+2') or a 7 day cytarabine continuous infusion plus daunorubicin for 3 days ('7+3');

- If <5% bone marrow blasts and per investigator judgement: consolidation cytarabine or post remission HSCT with either or both of the following:

    - Consolidation with single-agent cytarabine 3 g/m^2 IV for adults <60 years and 1 g/m^2 for adults ≥60 years over 3 hours twice daily (BID) on Days 1, 3, and 5, every 28 days for up to 4 cycles or alternative single-agent cytarabine consolidation schedules may be used per local prescribing information.

    - HSCT per standard of care.

A total of 267 death events would provide 90% power to detect an improvement in overall survival from 21 months to 31.5 months assuming a composite mOS for the population as follows: young AML (aged ≤60 years) with a mOS of 23.7 months and elderly AML (aged >60 years) with a mOS of 15 months[17,18] and with an HR=0.67 using a 1-sided log-rank test at a significance level of 0.025 and a 3-look group-sequential design.

Two interim analyses will be conducted: an early interim analysis of OS after 50% death events occur (no plan to stop for efficacy even if the efficacy boundary is crossed) and an efficacy and futility analysis of OS after 70% death events occur in the Intensive Chemotherapy population or upon completion of enrollment, whichever is later.

Non-Intensive Chemotherapy Study:

Subjects will be stratified at randomization by genetic risk (favorable vs intermediate vs adverse by ELN genetic risk categories)[16] and age (<75 years vs ≥75 years).[9,40]

A total of 320 subjects who are not candidates to receive Intensive Chemotherapy will receive treatment as follows:

- Experimental Therapy: Glasdegib 100 mg PO QD or matching placebo is to be administered by mouth daily beginning on Day 1 of chemotherapy and will continue if subjects demonstrate reasonable evidence of clinical benefit and do not meet the criteria for progression regardless of any delays/modifications in the chemotherapy treatment. Subjects will continue glasdegib or placebo until disease progression, unacceptable toxicity, consent withdrawal, or death, whichever comes first.

- Azacitidine will be administered by subcutaneous injection (SC) or intravenous (IV) infusion daily for 7 days, in 28 day cycles for as long as they do not meet the criteria for disease progression, unacceptable toxicity, consent withdrawal, or death, whichever comes first.

- Alternate dosing schedules to administer the 7 doses of azacitidine to accommodate patient and treatment center availability is allowed. Dose adjustments will be made according to local approved label for azacitidine. In addition, each subsequent cycle may be delayed for up to 28 days to allow for recovery of blood counts. Patients should continue to receive treatment as long as they do not meet the criteria for progression.

- Per Investigator discretion, HSCT may be performed. Glasdegib or placebo will be interrupted at least 28 days before HSCT Day 0 (day of stem cell infusion), and resumed 30-60 days post HSCT after documentation of ANC engraftment ($\geq 0.5 \times 10^9$/L for 3 consecutive days without growth factor support), no ongoing $\geq$ Grade 2 GVHD, and no ongoing SAEs that prevent resumption of glasdegib/placebo in the judgement of the Investigator. If therapy is resumed, glasdegib/placebo may continue up until 2 consecutive CR MRD-negative results, death or consent withdrawal.

- For patients undergoing HSCT, azacitidine may continue prior to HSCT, per the investigator discretion. Following HSCT, azacitidine will not be resumed.

A total of 220 death events would provide 90% power to detect an improvement in overall survival from 10.4 months[9] to 16.2 months with an HR=0.64 using a 1-sided log-rank test at a significance level of 0.025 and a 2-look group-sequential design. One interim efficacy and futility analysis of OS would be planned after 60% death events occur in the non-intensive chemotherapy population or upon completion of enrollment of these subjects, whichever is later.

The interim and final analyses of the intensive chemotherapy and non-intensive chemotherapy populations will be conducted separately and independent of each other.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

These criteria must also be met prior to dosing on Day 1. No exceptions will be granted.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Assignment to the Intensive Study or the Non-Intensive Study will be made by the Investigator based the 2017 ELN recommendations.[16]

The following eligibility criteria applies to subjects assigned to both the intensive study and the non-intensive study unless otherwise indication.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the Intensive and Non-Intensive study (unless where indicated):

1. Subjects with untreated AML according to the World Health Organization (WHO) 2016 Classification,[20] including those with:

    - AML arising from MDS or another antecedent hematologic disease (AHD).
    - AML after previous cytotoxic therapy or radiation (secondary AML).
    - FLT3+ AML, assuming the patient is not receiving and is not intended to receive FLT3 inhibitor therapy during study participation.

2. ≥18 years of age (In Japan, ≥20 years of age).

3. Adequate Organ Function as defined by the following:

    - Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN), excluding subjects with liver function abnormalities due to underlying malignancy.
    - Total serum bilirubin ≤2 x ULN (except subjects with documented Gilbert's syndrome).
    - Estimated creatinine clearance ≥30 mL/min as calculated using the standard method for the institution.

4. QTc interval ≤470 msec using the Fridericia correction (QTcF).

    - QTc criteria for eligibility does not apply to subjects with a functioning pacemaker, whether the rhythm is paced or not.

5. All anti-cancer treatments (unless specified) should be discontinued ≥2 weeks from study entry, for example: targeted chemotherapy, radiotherapy, investigational anti-cancer agents, hormones, or cytokines.

    - For control of rapidly progressing leukemia, hydroxyurea, and/or leukopheresis may be used before and for up to 1 week after the first dose of glasdegib. Continuation or resumption of hydroxyurea or leukopheresis after that time period must be approved by the Sponsor.

6. Serum or urine pregnancy test (for female subjects of childbearing potential) with a minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin (hCG) negative at screening.

7. Male and female subjects of childbearing potential and at risk for pregnancy must agree to use at least one highly effective method of contraception throughout the study and for 180 days after the last dose of azacitidine, cytarabine, or daunorubicin; and the last dose of glasdegib or placebo, whichever occurs later.

8. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

    a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    b. Have medically confirmed ovarian failure; or

    c. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the postmenopausal state.

        All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

9. Consent to a saliva sample collection for a germline comparator, unless prohibited by local regulations or ethics committee (EC) decision.

10. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

11. Subjects who are willing and able to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures (including bone marrow [BM] assessments).

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Acute Promyelocytic Leukemia (APL) and APLwith PML-RARA subjects (WHO 2016 classification).[1] This disease is associated with t(15;17).

2. AML with known BCR-ABL1 mutation or known t(9;22)(q34;q11.2) as a sole abnormality.

    - Complex genetics may include t(9;22) cytogenetic translocation.

3. Subjects with known active CNS leukemia.

4. Participation in other clinical studies involving investigational drug(s) other than anti-cancer agents (Phases 1-4) within 4 weeks prior study entry and/or during study participation.

5. Subjects known to be refractory to platelet or packed blood red cell transfusions per Institutional Guidelines, or a patient who refuses blood product support.

6. Subjects with another active malignancy on treatment with the exception of basal cell carcinoma, non-melanoma skin cancer, cervical carcinoma-in-situ. Other prior or concurrent malignancies will be considered on a case-by-case basis.

7. Any one of the following ongoing or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, symptomatic arrhythmias (including sustained ventricular tachyarrhythmia), left bundle branch block or bifascicular block, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism; as well as bradycardia defined as <50 bpm.

8. Subjects with an active, life threatening or clinically significant uncontrolled systemic infection not related to AML.

9. Subjects with left ventricular ejection fraction (LVEF) <50% are excluded from the Intensive Chemotherapy Study only.

10. Cumulative anthracycline dose equivalent of ≥550 mg/m2 of daunorubicin for the Intensive Chemotherapy Study only.

11. Known malabsorption syndrome or other condition that may significantly impair absorption of study medication in the investigator's judgment (eg, gastrectomy, lap band, Crohn's disease) and inability or unwillingness to swallow tablets or capsules.

12. Current use or anticipated requirement for drugs that are known strong CYP3A4/5 inducers (Appendix 5).

13. Concurrent administration of herbal preparations.

14. Major surgery within 4 weeks of starting study treatment.

15. Documented or suspected hypersensitivity to any one of the following:

    - For subjects assigned to intensive chemotherapy, documented or suspected hypersensitivity to cytarabine (not including drug fever or exanthema, including known cerebellar side-effects) or daunorubicin.

    - For subjects assigned to non-intensive chemotherapy, documented or suspected hypersensitivity to azacitidine or mannitol.

16. Known active drug or alcohol abuse.

17. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

18. Pregnant females or breastfeeding female subjects.

19. Known recent or active suicidal ideation or behavior.

20. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

4.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not randomized. A minimum set of screen failure subject data, should be collected to ensure transparent reporting of screen failure subjects.

4.4. Lifestyle Requirements

4.4.1. Contraception

In this study, male subjects who are able to father children and female subjects who are of childbearing potential will receive glasdegib, a compound which has been associated with teratogenic risk. Subjects treated with the non-intensive therapy will receive azacitidine, a compound that has been shown to cause congenital malformations in animals. Subject's ability to father or bear children must be assessed by the investigator at the time of screening and documented in the subject's chart. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least 1 highly effective form of contraception throughout the study and for at least 180 days after the last dose of investigational product as defined in Table 6.

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected at least 1 appropriate method of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use at least 1 highly effective method of contraception consistently and correctly and document the conversation, and the subject's affirmation, in *the subject's* chart. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner(s).

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the methods described in Table 6.

4.4.2. Postmenopausal Defined

Postmenopausal female

A postmenopausal state is defined as age 60 or older or no menses for 12 months without an alternative medical cause.

- A high follicle stimulating hormone (FSH) level in the postmenopausal range (as per the reference range used by the laboratory) may be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or hormonal replacement therapy (HRT).

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

Table 6. Contraceptives Allowed During the Trial

Highly effective (failure rate <1% if used consistently and correctly) low user dependency	Highly Effective (Failure rate <1% if used consistently and correctly) high user dependency
1. Implantable progestogen only contraceptive implant associated with inhibition of ovulation. 2. Intrauterine hormone releasing system (IUS). 3. Intrauterine device (IUD). 4. Bilateral tubal occlusion. 5. Vasectomized partner: A vasectomized partner is a highly effective form of contraception provided they are the sole male partner of the WOCBP and the absence of sperm has been confirmed. If not an additional highly effective method of contraception should be used.	1. Combined hormonal contraception (estrogen and progestogen). • Oral. • Intravaginal. • Transdermal. • Injectable. 2. Progestogen only hormonal contraception. • Oral; or • Injectable. 3. Sexual abstinence. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this trial. Male condom and female condom should not be used together (due to risk of failure with friction).	

4.5. Sunlight Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the subjects' exposure to light including high intensity ultraviolet B light (UVB) sources such as tanning beds, tanning booths and sunlamps. Subjects should be encouraged to apply sunscreen/sunblock daily.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the investigator file.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a help desk in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's

participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this protocol, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

- For this study, the investigational products are glasdegib, azacitidine, daunorubicin, and cytarabine.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) System [Interactive Web Response (IWR)/Interactive Voice Response (IVR)]. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, protocol number and the date of birth of the subject. The site personnel will then be provided with a treatment assignment and dispensable units (DU) or container number(s) when drug is being supplied via the IRT. The IRT system will provide a confirmation report containing the subject identification number and DU(s) or container number(s) assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Glasdegib or matching placebo treatment allocation will be blinded to the subject, investigator, and the study team. Randomization will be stratified according the stratification factors described in Section 9.3.1.

5.2. Breaking the Blind

The study will be subject and investigator blinded.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment are encouraged to discuss with a member of the study team if they believe that unblinding is necessary, unless this could delay further management of the participant. The date and reason that the blind was broken must be recorded in the source documentation.

Treatment allocation will be subject, investigator and sponsor blinded. There is no plan to break the blind upon subject progression or permanent discontinuation from study treatment. Blinding codes may be broken in emergency situations for reasons of subject safety.

NOTE: Once the blind is broken for a given patient, the patient will no longer be able to receive additional study treatment, follow-up and long-term follow-up are expected.

5.3. Subject Compliance

For glasdegib/placebo, all subjects will maintain subject dosing diaries throughout the study which will record the date of administration and all regular, missed, changed, or delayed doses.

Subjects are required to return all bottles, unused study drug and the subject dosing diary, at each cycle (or Day 1 of Induction(s)) and at End of Treatment visit for compliance assessment and drug accountability.

The number of tablets returned by the subject at the end of the cycle or Induction(s) will be counted, documented and recorded.

For azacitidine, daunorubicin, and cytarabine, the site should complete the required dosage Preparation Record located in the Investigational Product Manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose including the methodology used to calculate the subject body surface area (BSA). This may be used in place of the Preparation Record after approval from the Sponsor.

5.4. Investigational Product Supplies

5.4.1. Formulation, Packaging, Preparation, and Dispensing

5.4.1.1. Glasdegib/Placebo

Glasdegib will be supplied by Pfizer Worldwide Research and Development as 25 mg and 100 mg tablets for oral administration. Matching placebo tablets will also be provided. Supplies will be labeled according to local regulatory requirements.

Glasdegib and the matching placebo will be packaged in high-density polyethylene (HDPE) bottles and should be handled with care. Each bottle will contain enough medication for a 28-day cycle of daily dosing, plus an additional amount to cover the time between site visits. Subjects should be instructed to keep their medication in the bottles provided and not transfer it to any other containers and return the bottles to the site at the next study visit. Site personnel must ensure that subjects clearly understand the directions for self-medication.

Investigational product should be dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.4.1.2. Azacitidine

Central supply (provided by Pfizer) or locally obtained commercial supplies of azacitidine will be used in accordance with local regulations. Azacitidine is available as a vial containing 100 mg of powder for suspension for injection. Please refer to the local package insert (or SPC) or the Investigational Product Manual for detailed formulation information as well as SC or IV preparation and administration instructions.

5.4.1.3. Cytarabine

Central supply (provided by Pfizer) or locally obtained commercial supplies of cytarabine will be used in accordance with local regulations. Please refer to the local package insert (or SPC) or the Investigational Product Manual for detailed formulation, preparation for IV administration instructions.

5.4.1.4. Daunorubicin

Central supply (provided by Pfizer) or locally obtained commercial supplies of daunorubicin will be used in accordance with local regulations. Please refer to the local package insert (or SPC) or the Investigational Product Manual for detailed formulation, preparation and IV administration.

5.5. Administration

5.5.1. General Administration Guidance for Study Drugs

Bone marrow evaluations are performed at specific times to determine clinical response and treatment progression decisions within the trial. Bone marrow assessments are described in the Schedule of Activities for Intensive Chemotherapy (Table 1, Table 2) and for Non-Intensive Chemotherapy (Table 3, Table 4).

For subjects receiving chemotherapy, all subjects should be weighed within 72 hours prior to dosing for every cycle (or start of Induction 1, 2) to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of azacitidine, cytarabine, or daunorubicin required for dose preparation. Decision to recalculate chemotherapy dose based on the weight obtained at each cycle (or start of Induction 1, 2) can be in accordance with institutional practice for changes in weight of 10% or less; however if the subject experienced either a weight loss or gain of >10%, the amount of chemotherapy

required for study drug preparation and administration must be recalculated using this most recent weight/BSA obtained.

5.5.1.1. Glasdegib or Placebo in Subjects Receiving Intensive Chemotherapy and Non-Intensive Chemotherapy

Study treatment (glasdegib or placebo) will be administered by mouth at a starting dose of 100 mg daily at approximately the same time each day, preferably in the morning with approximately 8 ounces (240 ml) of water. Study treatment can be administered with or without food. Tablets must not be crushed or cut; they must be swallowed whole and not chewed.

A cycle is defined as 28 days, in the Non-Intensive Chemotherapy study. There is up to a 28 day window to coincide with azacitidine administration; dose delays due to toxicity will not impact the cycle duration or planned protocol assessments.

If a subject forgets to take their dose at the regularly scheduled time, and if less than 10 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible. If more than 10 hours have passed since the scheduled dosing time, the dose should be skipped and the subject should continue on their normal dosing schedule. If a subject misses a day's dose entirely, they must be instructed not to "make it up" the next day. Missed doses will NOT be made up at any time. If a subject vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a subject inadvertently takes one extra dose during a day, the subject should not take the next day's dose of glasdegib or placebo.

During the intensive chemotherapy study, glasdegib/placebo dosing will begin on Day 1 and be given once daily continuously in combination with Induction and Consolidation chemotherapy. Glasdegib or placebo will continue to be administered for a maximum of 2 years (starting from randomization until 2 years) or until subject discontinues per Section 6.5, or until confirmed CR MRD negative with two consecutive central laboratory results post consolidation.

During the non-intensive chemotherapy study, glasdegib or placebo dosing will begin on Day 1 and will be given once daily with azacitidine in 28 day cycles or until subject discontinues per Section 6.5, or is confirmed CR MRD negative by two consecutive central lab results post HSCT.

5.5.1.2. Intensive Chemotherapy

Refer to the local package inserts (or SPC) or Investigational Product Manual for detailed formulation, preparation and dispensing information for cytarabine and daunorubicin.[38,39] An overview of the treatment algorithm is shown in Figure 2 and specific doses and dosing frequencies are provided in Table 7.

Figure 2. Intensive Chemotherapy Treatment Algorithm: Glasdegib or Placebo in combination with Cytarabine and Daunorubicin

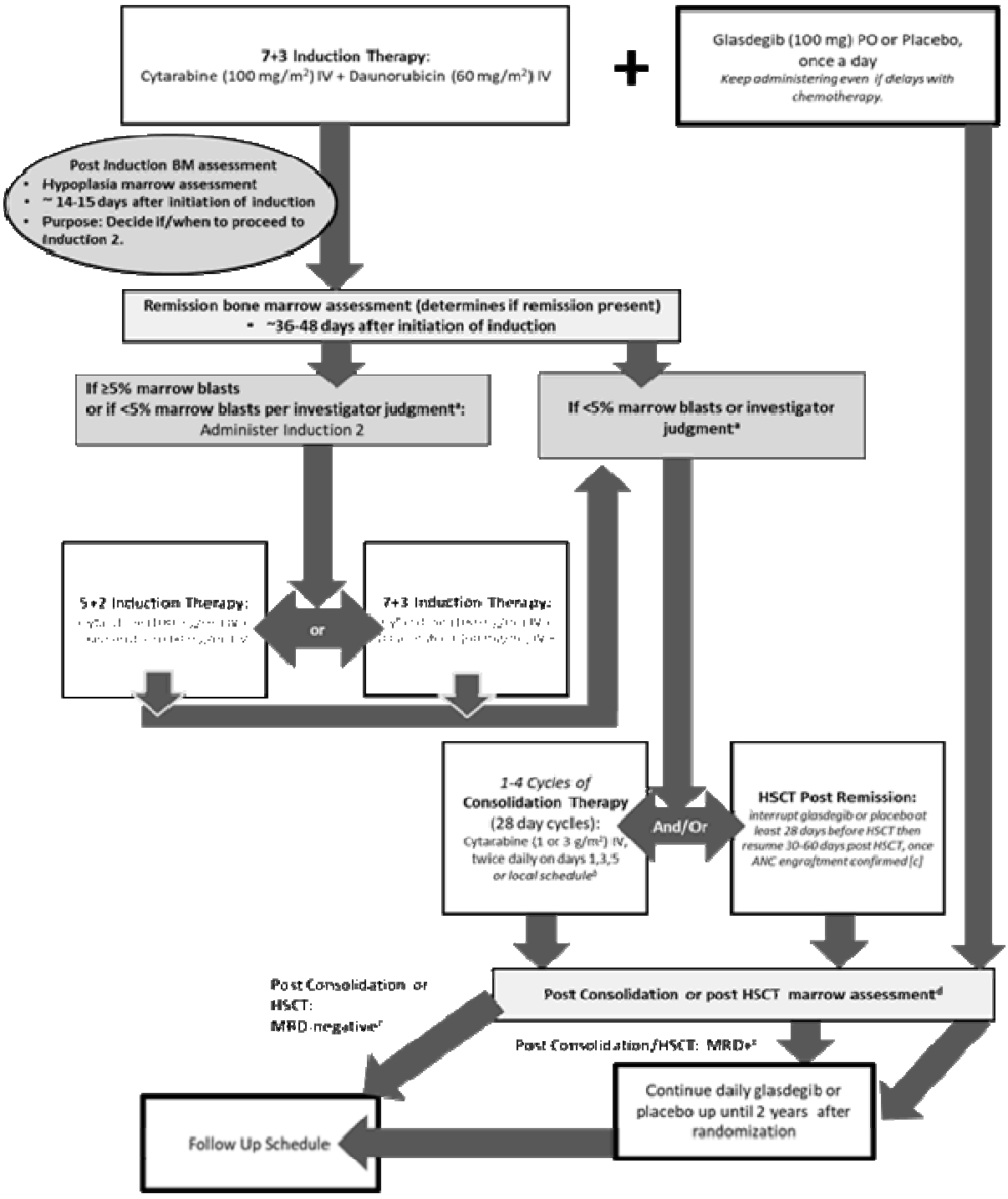


Figure footnotes:

a. If <5% bone marrow blasts, the investigator may either treat with a second Induction therapy or proceed to Consolidation therapy with single-agent cytarabine and/or post remission HSCT.

b. Consolidation with cytarabine 3 g/m^2 IV for adults <60 years and 1 g/m^2 for adults ≥60 years over 3 hours twice daily (BID) on Days 1, 3, and 5, every 28 days for up to 4 cycles. Alternative single-agent cytarabine consolidation schedules may be used per local prescribing information.

c. Resume glasdegib or placebo 30-60 days post day of stem cell infusion, once there is confirmed ANC engraftment (≥0.5 x 10^9/L) for 3 consecutive days with no growth factor support, no ≥Grade 2 ongoing GVHD, and no ongoing SAEs that prevent resuming glasdegib or placebo in the judgment of the investigator. Following Post Consolidation or Post Remission HSCT, modify treatment based on 2 matching and consecutive MRD negative results (by central laboratory) when they are available.

d. Post consolidation bone marrow assessment should be conducted after chemotherapy-based consolidation period. For patients proceeding to HSCT, post-HSCT bone marrow assessment will be conducted approximately 3 months after HSCT. This post-HSCT bone marrow assessment may be later than the resumption of glasdegib/placebo 30-60 days post HSCT.

Glasdegib or Placebo

Experimental Therapy: Glasdegib 100 mg PO QD or matching placebo will be administered by mouth daily beginning on Day 1 and is to continue up to 2 years post randomization until treatment failure, hematologic relapse, objective disease progression, patient refusal, unacceptable toxicity, unexpected pregnancy, death, or consent withdrawal.

- Subjects will receive daily glasdegib 100 mg PO or matching placebo up to 2 years after randomization or until they have CR MRD-negative disease post consolidation. Glasdegib or placebo therapy will continue throughout Induction(s) and Consolidation Therapy regardless of any delays/modifications in the chemotherapy treatment.

Cytarabine

- Separate cytarabine dosing and schedules will be used for Induction and Consolidation per the local package insert (or SPC) or Investigational Product Manual (or SPC).

    - **Induction 1**: Cytarabine will be administered (in parallel to daunorubicin) at a dose of 100 mg/m^2 daily by continuous IV infusion for 7 days (Days 1-7).

    - **Induction 2**, if indicated based on ≥5% marrow blasts (or investigator judgment if <5% bone marrow blasts), The Investigator may choose either cytarabine 100 mg/m^2 IV daily on Days 1-5 or Days 1-7. Dose must be recalculated if the weight changes by >10%.

Daunorubicin Dosing (Induction Only):

- During **Induction 1**, daunorubicin 60 mg/m^2 daily IV on Days 1-3.

- **Induction 2,** if indicated based on ≥5% bone marrow blasts (or investigator judgment if <5% bone marrow blasts), the Investigator will choose either daunorubicin 60 mg/m^2 IV daily on Days 1-2 or Days 1-3 with cytarabine. If clinical signs or symptoms of cardiac dysfunction are observed, multigated acquisition scan/echocardiogram (MUGA/ECHO) must demonstrate a LVEF ≥45% before initiation of Induction 2. Dose must be recalculated if the weight changes by >10%.

- If <5% bone marrow blasts: treatment with either or both of the following if a second Induction is not selected (per investigator judgment):

  - Consolidation with single-agent cytarabine 3 g/m^2 IV for adults <60 years and 1 g/m^2 for adults ≥60 years over 3 hours twice daily (BID) on Days 1, 3, and 5, every 28 days for up to 4 cycles or alternative single-agent cytarabine consolidation schedules may be used per local prescribing information.

  - HSCT per local standard of care.

A detailed dosing schedule is found in Table 7.

Table 7. Intensive Chemotherapy Doses and Dose Frequency: Glasdegib or Placebo in Combination with Daunorubicin and Cytarabine

Days	Induction Therapy	
	Backbone Chemotherapy[a]	**Experimental Therapy**[a,b,c]
1-3	Administer Daunorubicin 60 mg/m^2 IV Administer cytarabine 100 mg/m^2 IV	Administer glasdegib 100 mg PO or placebo PO
4-7	Administer cytarabine 100 mg/m^2 IV	
≥8[d]		
Days	**Second Induction if ≥5% bone marrow blasts or investigator judgement for <5% bone marrow blasts (Option 1: '5+2')**	
	Backbone Chemotherapy[a]	**Experimental Therapy**[a,b,c]
1-2	Administer Daunorubicin 60 mg/m^2 IV Administer cytarabine 100 mg/m^2 IV	Administer glasdegib 100 mg PO or placebo PO
3-5	Administer cytarabine 100 mg/m^2 IV	
≥6[d]		
Days	**Second Induction if ≥5% bone marrow blasts or investigator judgement for <5% bone marrow blasts (Option 2: '7+3')**	
	Backbone Chemotherapy[a]	**Experimental Therapy**[a,b,c]
1-3	Administer Daunorubicin 60 mg/m^2 IV Administer cytarabine 100 mg/m^2 IV	Administer glasdegib 100 mg PO or placebo PO
4-7	Administer cytarabine 100 mg/m^2 IV	
≥8[d]		
Days	**If <5% bone marrow blasts, Consolidation (Option 1): 1-4 Cycles of Consolidation (28 day cycles)**	
	Backbone Chemotherapy[a]	**Experimental Therapy**[a,b]
1	Administer cytarabine 1or 3 g/m^2 IV twice daily (BID)	Administer glasdegib 100 mg PO or placebo PO
2		

Table 7. Intensive Chemotherapy Doses and Dose Frequency: Glasdegib or Placebo in Combination with Daunorubicin and Cytarabine		
3	Administer cytarabine 1or 3 g/m^2 IV twice daily (BID)	
4		
5	Administer cytarabine 1or 3 g/m^2 IV twice daily (BID)	
≥6[d]		
Up to 2 years after randomization[d]		
Timing	**If <5% bone marrow blasts, Consolidation (and/or Option 2): HSCT**	
	Chemotherapy containing regimen	**Experimental Therapy**[a,b]
At least 28 days before HSCT (Day 0)		Interrupt all study therapy.
Confirmed ANC engraftment, 30-60 days post HSCT[e]		Administer glasdegib 100 mg PO or placebo PO

a. Instructions for glasdegib/placebo dose modifications and Intensive chemotherapy are in Section 5.5.5. Consolidation with cytarabine 3 g/m^2 IV for adults <60 years and 1 g/m^2 for adults ≥60 years over 3 hours twice daily (BID) on Days 1, 3, and 5, every 28 days for up to 4 cycles. Alternative single-agent cytarabine consolidation schedules may be used per local prescribing information.

b. Treatment with glasdegib should continue during any delay before the start of another cycle or Induction in the absence of glasdegib-related toxicity that would prevent dosing.

c. Where possible, glasdegib will be administered together with daunorubicin IV injection during induction.

d. Glasdegib or placebo is administered up to 2 years after randomization unless there is progression, unmanageable toxicity, withdrawal of consent, or CR MRD-negative disease confirmed at 2 consecutive time points post consolidation.

e. Confirmed ANC engraftment is defined by ANC ≥0.5 x 10^9/L for 3 consecutive days with no growth factor support following HSCT using myeloablative or non-myeloablative conditioning regimen. 30-60 days post HSCT, glasdegib or placebo may be resumed with ANC engraftment, no ≥ Grade 2 ongoing GVHD, and no ongoing SAEs that prevent resuming glasdegib or placebo maybe present, in the judgement of the investigator.

Induction for Intensive Chemotherapy Study

Subjects will participate in their first induction therapy for a total of 28 days. However, if a subject requires a second Induction therapy due to residual leukemia or investigator opinion, this second course may start as soon as possible following Induction 1 bone marrow evaluation.

If the induction cycle(s) extends longer than 28 days, dosing with glasdegib or placebo should continue daily in the absence of glasdegib-related toxicity that would prevent dosing.

The second induction may be delayed up to an additional 28 days from Day 28 of the first induction to allow for the subject to recover from any severe reversible hematologic or non-hematologic drug related toxicity. Treatment with glasdegib or placebo should continue during any delay before the start of the second induction in the absence of glasdegib-related toxicity that would prevent dosing. The second induction should not be performed if the subject has clinically significant cardiotoxicity (LVEF <45%) and the subject should be discontinued from treatment.

Bone marrow may be repeated at Investigator discretion as required for clinical staging any time prior to next Induction chemotherapy.

The following rules apply for progression from induction to consolidation (Table 7):

a. Subjects who successfully obtain a <5% bone marrow blasts after induction are eligible to enter the consolidation phase of the trial 28-days from the start of the last induction. These subjects may also proceed to a second Induction per investigator judgment;

b. Subjects with residual leukemia at the end of induction 1 may be treated with a second induction therapy;

c. If after the second induction, the subject still shows residual or resistant leukemia, they must be discontinued from treatment and followed as described in Section 5.5.2. Subjects with resistant leukemia after the first or second course of induction will be discontinued from treatment and followed as described in Section 5.5.2.

Precise timings for the post first induction bone marrow assessment and remission assessment will depend on investigator judgement. In general:

- The **post first induction bone marrow assessment** will occur approximately 14-15 days after initiation of first induction therapy; however, the precise timing will be according to investigator judgment. The post first induction bone marrow assessment is generally done to assess marrow hypoplasia and determine if/when a second Induction is needed. Following the post first induction bone marrow assessment, subjects may complete Induction 1 therapy, start Induction 2 before finishing Induction 1, or end treatment and go to follow-up.

- The remission bone marrow assessment usually occurs approximately 36-48 days after initiation of induction therapy. However, these timings will depend on investigator judgement. The remission bone marrow assessment is generally done to assess hematologic response following Induction therapy. Hematological response will be assessed using the bone marrow results from the remission bone marrow assessment.

Consolidation Therapy with a Chemotherapy-containing regimen

Subjects achieving <5% bone marrow blasts, after the completion of induction therapy are eligible to begin consolidation. Glasdegib will continue to be given at the dose given during induction (unless dose modification due to toxicity is required) once daily in the morning continuously in 28-day cycles, where possible at the same with chemotherapy infusion start.

Subjects can remain on study for a minimum of one but not more than four courses of consolidation if they do not progress during consolidation treatment. If a subject enters consolidation with a CRi (post induction) assessment but then achieves hematologic recovery in the peripheral blood (defined as ANC >1000/μL and platelets ≥100,000/μL), the bone marrow evaluation should be repeated within 14 days of the hematologic recovered blood counts observation. Bone marrow examinations may be performed at any time throughout consolidation as clinically indicated to confirm the subject has not relapsed. At a minimum a bone marrow evaluation is required following the final consolidation cycle before any subsequent therapy.

The start of subsequent consolidation cycles may be delayed from the end of the previous cycle to allow for recovery from reversible hematologic or non-hematologic drug-related toxicities. If the consolidation cycle(s) extends longer than 28 days, dosing with glasdegib or placebo should continue daily in the absence of glasdegib-related toxicity that would prevent dosing.

Post Remission HSCT

Subjects who are eligible for Post Remission HSCT will undergo HSCT per local standard of care. For HSCT, Day 0 is the first day of HSCT; this is the day when stem cells are infused.

For post remission HSCT, glasdegib or placebo will be interrupted at least 28 days before HSCT and resumed 30-60 days post date of stem cell infusion, once there is ANC engraftment, no ≥ Grade 2 ongoing GVHD, and no ongoing SAEs that prevent resuming glasdegib/placebo in the judgement of the investigator. Confirmed ANC engraftment is defined by ANC $\geq 0.5 \times 10^9$/L for 3 consecutive days without growth factor support following HSCT using myeloablative or non-myeloablative conditioning regimen.

Post Consolidation or Post HSCT treatment

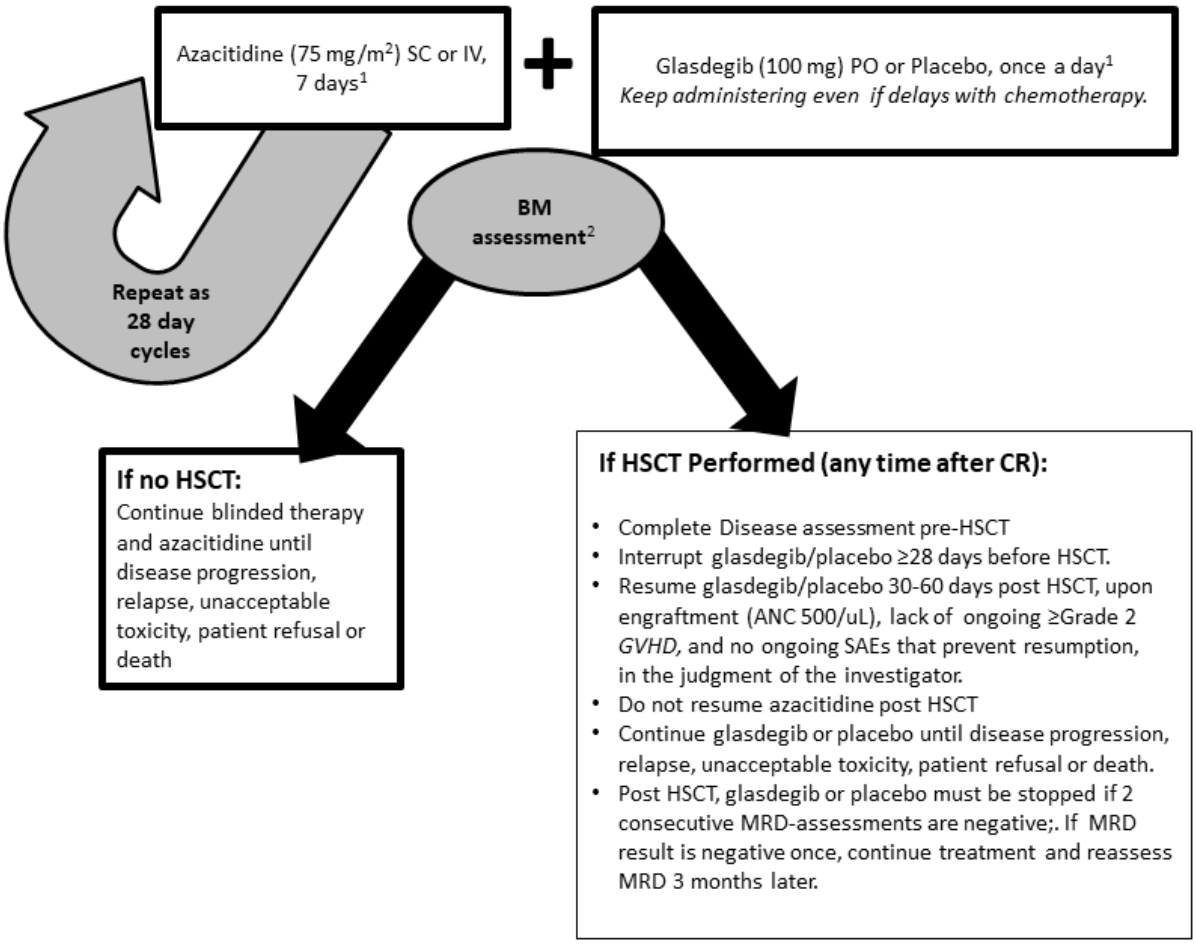
Daily glasdegib (100 mg) PO or placebo PO may continue up to 2 years following randomization unless AML is confirmed MRD negative post Consolidation or post HSCT MRD at 2 consecutive time points per central laboratory analysis. These 2 consecutive time points may be approximately 3 months apart as part of the already scheduled marrow assessments.

5.5.1.3. Non-Intensive Chemotherapy

For subjects in the Non-Intensive Chemotherapy study, central supply (provided by Pfizer) or locally obtained commercial supplies of azacitidine will be used. Refer to the local package insert (or SPC) or Investigational Product Manual (or SPC) for detailed formulation, preparation and dispensing information.[33]

The general treatment algorithm for the Non-Intensive study is described in Figure 3.

Figure 3. Non- Intensive Chemotherapy Treatment Algorithm: Glasdegib or Placebo in combination with Azacitidine



1. Details for azacitidine administration with glasdegib or placebo are described in Table 8.

2. A bone marrow assessment is required when CR is suspected or after end of Cycle 6; whichever, is earlier. BM aspirate is required, and biopsy is preferred. Following Cycle 6, BM assessments will occur when there is an intention for patient to receive HSCT, progressive disease (PD) suspected.

Table 8. Non-Intensive Chemotherapy: Glasdegib or Placebo in Combination with Azacitidine

Days	Study Treatment[a]	
	Chemotherapy	**Experimental Therapy**
1-7 (±3 day window for each dose)	Administer azacitidine 75 mg/m^2 SC or IV	Administer glasdegib 100 mg PO or placebo PO
8-28		Administer glasdegib 100 mg PO or placebo PO
Repeat[b]	Repeat administration of azacitidine 75 mg/m^2 SC or IV for 7 days as 28 day cycles[a]	Administer glasdegib 100 mg PO or placebo PO
Timing	**If proceeding to HSCT per local Standard of Care**	
At least 28 days before HSCT (Day 0)	Interrupt Glasdegib/placebo.	
30-60 days post HSCT[c]	Resume administration of Glasdegib 100mg PO or Placebo PO[d]	

a. See Section 5.5.5 for recommended dose modifications/delays/reductions. Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles, or until unacceptable toxicity, patient refusal or death, whichever occurs first. Treatment will be administered in a 28 day cycle, but cycle duration may be extended to allow for toxicity resolution.

b. Treatment with the study drug combination should be continued beyond 6 cycles of treatment until objective disease progression or relapse, unacceptable toxicity, patient refusal or death, whichever occurs first.

c. Confirmed ANC engraftment is defined by ANC $\geq 0.5 \times 10^9$/L for 3 consecutive days with no growth factor support following HSCT using myeloablative or non-myeloablative conditioning regimen. 30-60 days post HSCT, glasdegib or placebo may be resumed with ANC engraftment, no $\geq$ Grade 2 ongoing GVHD, and no ongoing SAEs that prevent resuming glasdegib or placebo may be present, in the judgement of the investigator.

d. Glasdegib or placebo is administered up to 2 years after randomization unless there is progression, unmanageable toxicity, withdrawal of consent, or CR MRD-negative disease confirmed at 2 consecutive time points post consolidation.

Subjects will receive either glasdegib 100 mg PO once daily or matching placebo starting on Day 1 and continuing beyond 6 cycles of treatment until objective disease progression or relapse, unacceptable toxicity, patient refusal or death, whichever occurs first.

Azacitidine will be administered per local label or per the Investigational Product Manual (or SPC). The dose for azacitidine is 75 mg/m^2 daily for 7 days to be administered by SC injection or IV infusion in 28 day cycles. Alternate dosing schedule to administer the 7 doses to accommodate subject and treatment center availability is allowed. Dose adjustments will be made according to local approved label or per the Investigational Product Manual (or SPC) for azacitidine.

Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination will be continued for **at least 6 cycles**, or until unacceptable toxicity, patient refusal or death, whichever occurs first. In addition, each subsequent cycle may be delayed for up to 28 days to allow for recovery of blood counts. Subjects should continue to receive treatment beyond the Cycle 6, as long as they do not have uncontrollable toxicity, withdrawal consent, and do not meet the criteria for progression.

HSCT following CR

Subjects who are eligible HSCT will undergo HSCT per local standard of care. For HSCT, Day 0 is the first day of HSCT; this is the day when stem cells are infused.

For post remission HSCT, glasdegib or placebo will be interrupted at least 28 days before HSCT and resumed 30-60 days post date of stem cell infusion, once there is ANC engraftment, no ≥ Grade 2 ongoing GVHD, and no ongoing SAEs that prevent resuming glasdegib/placebo in the judgement of the investigator. Confirmed ANC engraftment is defined by ANC ≥0.5 x 10^9/L for 3 consecutive days without growth factor support following HSCT using myeloablative or non-myeloablative conditioning regimen.

Transplant-related information; such as, donor source, type of transplant, and conditioning regimen, must be entered into the CRF.

The HSCT Post Remission Period (HSCT period) is defined as time from the start of the conditioning regimen until the subject restarts glasdegib or placebo, death, post study follow-up, or withdrawal. During the HSCT Consolidation Period, AE collection during the HSCT period is defined in Section 8.

Post Consolidation or Post HSCT treatment

Daily glasdegib (100 mg) PO or placebo PO may continue up to 2 years following randomization unless AML is confirmed MRD negative post HSCT at 2 consecutive time points per central laboratory analysis. These 2 consecutive time points will be approximately 3 months apart as part of the already scheduled marrow assessments.

5.5.2. End-of-Treatment Follow-up

After discontinuation of study treatment (all arms), post-treatment survival status, response assessments (for those in remission), and hematologic relapse/disease progression will be collected as described in Table 1 and Table 2 for subjects receiving Intensive Chemotherapy and in Table 3 and Table 4 for subjects receiving Non-Intensive Chemotherapy until death or until termination of the study by the Sponsor.

Post treatment follow up visits will occur for the first 2 years. Subjects will return to the site for visits every 3 months starting from the last dose of study medication, for the first 2 years only.

A post treatment long-term follow-up will be completed ≥3 years starting from the last post treatment follow up visit. A telephone log will include the date of contact and survival data (including date and cause of death) and where possible, subsequent anticancer therapies, including HSCT.

The study will be considered complete once all subjects have been followed for survival for up to 5 years from the first dose of the last subject enrolled in the study, or until death, or consent withdrawal.

5.5.3. Food Requirements

Glasdegib will be administered with a glass of water, with or without food.

5.5.4. Treatment Discontinuation

If a subject demonstrates unequivocal clinically significant disease progression or unacceptable toxicity, they must be discontinued from treatment and followed as described in Section 6.4.

If glasdegib/placebo is permanently discontinued for reasons other than treatment failure, hematologic relapse, objective disease progression, subject refusal, or consent withdrawal, single-agent treatment with azacitidine, or combination daunorubicin and cytarabine may be continued if, in the Investigator's judgment, a clinical benefit has been observed and following discussion between the Investigator and Sponsor.

In cases of unacceptable toxicity or pregnancy, the subject must be withdrawn from study drug combination and entered into the follow-up phase of the study.

When study treatment with both drugs of the study combination (glasdegib/placebo and azacitidine, or cytarabine and daunorubicin) is permanently discontinued, subjects will enter into the follow-up phase.

5.5.5. Dose Modifications

Every effort should be made to administer the study treatments at the planned dose and schedule.

5.5.5.1. Glasdegib or Placebo in Subjects Receiving Intensive Chemotherapy and Non-Intensive Chemotherapy

In the event of Grade 3 or Grade 4 non-hematologic, study-treatment-related toxicity, dosing may be delayed and/or dose reduced. The glasdegib dose should be reduced 1 dose level at a time, in increments of 25 mg (75 mg QD, 50 mg QD, in the form of 3 or 2 x 25 mg tablets respectively).

Glasdegib or placebo does not need to be delayed or dose reduced for hematologic, study-treatment-related toxicity.

Glasdegib or placebo may be interrupted or permanently discontinued for any reason as per good clinical practice. Glasdegib or placebo should be permanently discontinued if interruptions are for more than 28 **consecutive** days when not required by the protocol (ie, HSCT period).

Dose escalations will not be allowed following glasdegib/placebo dose reductions.

Dose modifications may occur in three ways:

- **Within a cycle or within Induction 1, 2**: Dosing interruption until adequate recovery followed by dose reduction (if required) of glasdegib during a given treatment cycle.

- **Between cycles or between Induction 1, 2:** The next treatment cycle may be delayed if toxicity from the preceding cycle persists.

- **In the next cycle or within the next Induction**: Dose reduction may be required based on toxicities experienced in the previous cycle.

When chemotherapy is given, a Cycle is determined by chemotherapy administration schedule. A Cycle is 28 days, but will be extended if there are dose delays or modifications in the chemotherapy backbone. For Induction, there is no cycle and this therapy is referred to as Induction 1 and Induction 2.

When glasdegib or placebo is given alone, it is always in a 28 day Cycle.

No crossover between treatment arms will be permitted as crossover could significantly impact the primary endpoint of overall survival. Investigators are discouraged from prescribing glasdegib after discontinuation of study therapy.

5.5.5.2. Dosing Interruptions for Glasdegib/placebo Non-hematological Toxicities

Subjects experiencing Grade 3 or 4 non-hematological toxicities potentially attributable to glasdegib or placebo should have their glasdegib or placebo treatment interrupted regardless of when it occurs in the cycle until the toxicity resolves or returns to baseline or ≤ Grade 1, as described in Table 9.

If these parameters have not been met following >28 consecutive days of dose interruption, glasdegib or placebo should be permanently discontinued. If glasdegib or placebo treatment is permanently discontinued, patients may continue single-agent treatment with daunorubicin, cytarabine, or azacitidine, if according to the investigator's judgment a clinical benefit has been observed, and following discussion between the investigator and the sponsor.

Table 9. Glasdegib or Placebo Dose Modifications for Non Hematologic Toxicities (Excluding QTc Prolongation, Muscle Spasms, and Myalgia)

Toxicity (NCI CTCAE version 4.03)	Glasdegib or Placebo
≥ Grade 3 toxicity (Nausea, vomiting, and/or diarrhea must persist at ≥ Grade 3 (despite maximal appropriate medical therapy) to require dose modification).	Hold study drug until toxicity has recovered to baseline or ≤ Grade 1. **First episode**: Decrease by 1 dose level. **Second episode**: Decrease by 1 dose level. **Third episode**: Permanently discontinue.
Potential DILI/Hy's Law (as defined in Section 8.4.2).	Interrupt glasdegib/placebo dosing. If an alternative cause is found, restarting of glasdegib/placebo at the same dose may be considered.
Confirmed DILI/Hy's Law (as defined in Section 8.4.2).	Glasdegib/placebo should be permanently discontinued.

Appropriate follow-up assessments should be implemented until adequate recovery (toxicity resolves or returns to baseline) occurs.

Depending on when the adverse event resolved, treatment interruption may lead to the patient missing all subsequent planned doses of glasdegib or placebo within the cycle. If the AE leading to treatment interruption recovers within the same cycle, re-commencement of dosing in that cycle is allowed. Glasdegib or placebo doses omitted for toxicity will not be replaced within that cycle (eg, cycles will not be prolonged beyond the 28 days in order to make up for any missed glasdegib or placebo doses during that cycle).

The need for a dose reduction at the time of treatment resumption should be based on the criteria outlined in Table 9, unless specifically agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction for glasdegib or placebo is applied in the same cycle, the patient must return to the clinic to receive a new supply of drug.

In the event of glasdegib or placebo treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) for a duration >28 days, the details of treatment resumption will be determined in consultation with the sponsor.Glasdegib/placebo dose modifications for mean QTcF (mQTcF) prolongation are outlined in Table 10.

Table 10. Glasdegib Dose Modifications for mean QTcF (mQTcF) Prolongation

CTCAE v 4.03	Grade 1	Grade 2	Grade 3**	Grade 4**
Electrocardiogram QT corrected (QTc) interval prolonged*	450-480 msec	481-500 msec	≥501 msec on at least two separate ECGs	QTc ≥501 msec or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

*The severity of QTc prolongation assessment is to be determined by calculating a mean QT of 3 consecutive ECGs performed approximately 2 minutes (but no longer than 5 minutes) apart using the Frederica correction method (mQTcF).
**Please see Section 8.4.1 for protocol specified SAE reporting requirement of Grade 3 or 4 mQTcF prolongation.

Category	Action	Grade 1	Grade 2	Grade 3	Grade 4
General management	Assess electrolyte levels and supplement as clinically indicated		X	X	X
	Review and adjust concomitant medications with known QTc interval-prolonging effects		X	X	X
ECG monitoring	Monitor ECGs at least weekly for 2 weeks following resolution of mQTcF prolongation to ≤480 msec		X	X	X
Initial glasdegib action	Discontinue and do not re-challenge				X
	Interrupt treatment			X	
	Continue treatment at same dose	X	X		
Resume glasdegib dosing	If **no** prior glasdegib dose interruption related to QTcF prolongation has occurred, resume at a reduced dose of 75 mg once daily when mQTcF interval returns to within 30 msec of baseline or ≤480 msec			X	
	If **one** prior glasdegib dose interruption related to QTcF prolongation has occurred, resume at a reduced dose of 50 mg once daily when mQTcF interval returns to within 30 msec of baseline or ≤480 msec			X	
Discontinue glasdegib permanently	If **two** prior glasdegib dose interruptions related to QTcF prolongation have occurred			X	

QTc criteria for dose modifications does not apply to subjects with a functioning pacemaker, whether the rhythm is paced or not. Dose modifications for glasdegib/placebo in case of drug class related AEs (muscle spasms, myalgia) are outlined in Table 11.

Table 11. Dose Modifications for glasdegib/placebo in Case of Drug Class Related AEs

Muscle Spasms or Myalgia	Grade 1	Grade 2	Grade 3
Glasdegib/ Placebo	Continue at same dose level. Administer oral rehydration solutions containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine.	Continue at same dose level. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine. If event persists, hold dose until resolution to Grade ≤1. Upon resolution, restart at prior dose, or for prolonged muscle spasms, consider reducing dose by one dose level.	Hold dose. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine. Upon resolution to Grade ≤1, restart study treatment at next lower dose level. If the event does not resolve within 3 weeks to Grade ≤1, at the discretion of the Investigator the dose may be restarted at the next lower dose level or the subject may be permanently discontinued from study treatment.

Abbreviations: CK creatinine kinase; Vit vitamin; Na sodium; K potassium; Mg magnesium; Ca calcium; P phosphorous.

a. Electrolyte replacement drinks should include Na, K, Mg, Ca and P. Consideration should be given to ensuring adequate hydration prior to bedtime, and whenever fluid intake is decreased for a prolonged duration.

b. Labs may be drawn as unscheduled assessments between protocol visits.

In the event of alopecia or dysgeusia, investigator discretion should be applied with respect to dose interruption and/or dose reduction of glasdegib/placebo as preliminary analysis of available clinical data suggests that these events are not dose dependent.

5.5.5.3. Intensive Chemotherapy and Non-Intensive Chemotherapy

For subjects in the Intensive Chemotherapy study, Central supply (provided by Pfizer) or locally obtained commercial supplies of daunorubicin and cytarabine will be used. Refer to the local package insert (or SPC) or Investigational Product Manual for dose modification criteria.

For subjects in the Non-Intensive Chemotherapy study, Central supply (provided by Pfizer) or commercially available azacitidine will be used (Section 5.4.1.2). Refer to the local package insert (or SPC) or Investigational Product Manual for dose modification criteria.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD (IB for PF-04449913 and EU SPC for Vidaza®,[33] EU SPC for Cytarabine,[38] and EU SPC for Daunorubicin)[39] will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products and how to report excursions.

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. At each dispensing visit (Cycle 2 Day 1, Cycle 3 Day 1, Induction 1, Induction 2, etc. or when there is a dose reduction), all unused or partially used bottles of glasdegib/placebo must be returned by patients to the Investigator. The number of tablets returned by the patient at the end of the cycle (or induction 1, 2) will be counted, documented and recorded.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

All concomitant medications and treatments must be recorded in the CRF except during the HSCT period from the first day of conditioning until a subject resumes glasdegib or placebo post HSCT. During this HSCT period, no concomitant medications (other than transplant conditioning regimen) will be collected. If a patient resumes glasdegib or placebo following HSCT, HSCT-related Medical History must be provided. This will include information regarding ongoing medical conditions and their associated concomitant medications that started from the first day of conditioning until the time of re-starting glasdegib or placebo therapy.

Any prior treatment received within 28 days prior to study entry (including hematopoietic growth factor receptor agonists: erythropoietin, granulocyte colony stimulating factor (G-CSF), romiplostim, eltrombopag) will be recorded in the CRF.

In addition, any transfusion (red blood cells or platelets) within 8 weeks prior to randomization should be recorded in the CRF for the non-intensive study only. Transfusions (red blood cells or platelets) will not be recorded during the HSCT period unless part of ongoing Medical History once they resume glasdegib/placebo.

All prior therapies used to treat AML will be recorded regardless of when they were received by the subject. Information collected will include dates of use, best treatment response and the reasons for stopping therapy.

Every concomitant treatment, blood products, growth factors, as well as interventions, required by the subjects during the active study treatment (and up to 28 days following last study drug administration or until initiation of another anti-cancer treatment) and the reason for its administration must be recorded on the CRF.

5.8.1. Restricted or Prohibited Concomitant Medications

The following medications are not allowed during the active study treatment period:

- Agents used to treat AML;
- Investigational agents;
- Concurrent administration of herbal preparations;
- CYP3A4/5 Inducers: A drug-drug interaction study in health subjects with the strong CYP3A4 inducer, rifampin, resulted in a 70% decrease in plasma exposures (AUC_{inf}) and a 35% decrease in peak plasma concentration (C_{max}) of a single 100-mg oral dose of glasdegib. Therefore co-administration of glasdegib and moderate/strong CYP3A4/5 inducers is not permitted. A comprehensive list of moderate/strong CYP3A4/5 inducers is provided in Appendix 5. However, if you are uncertain whether a concomitant medication is contraindicated, you should contact the Sponsor study team.

The following medications have use restrictions during the active study treatment period:

- CYP3A4/5 Inhibitors: In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2.4-fold increase in plasma exposure and a 1.4-fold increase in peak plasma concentration of glasdegib. Therefore a potential exists for drug-drug interactions with CYP3A4/5 inhibitors, and co-administration of glasdegib/placebo in combination with moderate/strong CYP3A4/5 inhibitors is not recommended. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Moderate/strong CYP3A4/5 inhibitors (Appendix 6 and Appendix 7) should be used with caution and only if considered medically necessary. If a moderate/strong CYP3A4/5 inhibitor is to be initiated in addition to glasdegib/placebo, the guidance provided in Section 7.1.7 and dose modifications for QT prolongation per Table 10 must be followed. If you

are uncertain whether a concomitant medication is a CYP3A4 inhibitor, you should contact the Sponsor study team.

- Drugs with a known risk of Torsade de pointes (TdP): Glasdegib has been shown to have the potential to prolong the QTc interval in pre-clinical studies. In the first-in-subject study as single agent, Grade 3 QTcF prolongation was observed at the highest doses tested (400 mg and 600 mg). While the glasdegib dose evaluated in this study is 100 mg, the concomitant administration of glasdegib and drugs with a known risk of Torsade de pointes should be avoided whenever possible. A list of such drugs is provided in Appendix 8. Use of these drugs is not recommended unless there are no alternatives. If a TdP drug is to be initiated in addition to glasdegib/placebo the guidance provided in Section 7.1.7 and dose modifications for QT prolongation per Table 10 must be followed.

- QT prolonging medications (without a risk of TdP) should be avoided whenever possible.

- Concomitant administration of multiple moderate/strong CYP3A4/5 inhibitors, TdP drugs, and/or QT prolonging medications (without a risk of TdP) is not recommended.

5.8.2. Permitted Concomitant Medications

5.8.2.1. Best Supportive Therapy

Best Supportive Therapy (BST) administration is permitted and encouraged according to Institutional guidelines for all subjects on study. BST will be provided by the site and may vary depending on the subject's signs and symptoms, site current practice, and country practice. It includes medications and supportive measures that may palliate disease-related symptoms, improve quality of life, prevent and treat bacterial, fungal or viral infections. BST may include:

- Blood transfusions;

- Platelet transfusions;

- Prophylactic antimicrobials (recommended particularly for intensive chemotherapy arm according to institutional guidelines);

- Antibiotics (Section 5.8.1);

- Anti-fungal agents (Section 5.8.1);

- Anti-viral agents (Section 5.8.1).

5.8.2.2. Hematopoietic Growth Factors

Hematopoietic growth factors may be used per local standard of care and per local labels.

5.8.2.3. Anti-Emetic and Anti-Diarrheal Therapy

Subjects should be pre-medicated with anti-emetics for nausea and vomiting before each dose of chemotherapy according to local practice and guidelines.

Primary prophylaxis of diarrhea is permitted at the Investigator's discretion. The choice of the prophylactic drug is up to the investigator.

5.8.2.4. Prophylactic Intrathecal Chemotherapy

Prophylactic intrathecal chemotherapy is allowed, per investigator discretion.

5.8.2.5. Corticosteroids

Chronic and acute administration of systemic and non-systemic corticosteroids (topical applications, inhaled sprays, eye drops or local injections) is allowed.

5.8.2.6. Surgery

Caution is advised for any surgical procedures during the study. The appropriate interval of time between surgery and glasdegib required to minimize the risk of wound healing and bleeding has not been determined. Stopping glasdegib is recommended at least 7 days prior to surgery. Post-operatively, the decision to reinitiate glasdegib treatment is up to the Investigator with Sponsor approval and should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

Screening can be accomplished over one or multiple visits over a 4-week period (28 days), unless specifically noted otherwise (ie, bone marrow sample collection). Protocol specific tests or procedures not considered standard of care can only be done after the subject has signed the Informed Consent document. The Informed Consent document may be signed up to 60 days prior to study entry.

See the Schedule of Activities for a complete list of assessments and procedures to be collected during the screening period.

6.2. Treatment Period

See the Schedule of Activities for a detailed list of the assessments and procedures to be collected. Study entry is defined as when the subject is randomized into the IRT system. Subjects must be randomized into the IRT system prior to receiving first dose of study drug.

All assessments on Day 1 of each cycle should be collected pre-dose, unless documented otherwise.

CCI [redacted]

In cases of unacceptable toxicity or pregnancy, the subject must be withdrawn from study drugs, have an end of treatment visit (Section 6.3), and be entered into the post-treatment follow-up phase (Section 6.4).

Subjects who permanently discontinue both study drugs (azacitidine or daunorubicin and cytarabine or glasdegib/placebo) for any reason (except death, or withdrawal of subject consent for follow-up) will enter into the follow-up phase of the study.

6.3. End of Treatment Visit

The End of Treatment Visit should be scheduled as soon as possible once a patient has been withdrawn from study drug. For a detailed list of assessments and procedures to be completed please refer to the Schedule of Activities.

Patients continuing to experience toxicity following discontinuation of treatment will be followed by the Investigator at least every 4 weeks until resolution or determination, in the Clinical judgment of the investigator, that no further improvement is expected.

6.4. Follow-up

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

Please refer to the Schedule of Activities for details on assessments to be completed during the 2 types of follow-up visits: post treatment follow-up visits (first 2 years following last dose of study medication) and long-term follow-up (≥3 years).

Subjects will be followed for survival for up to 5 years from the first visit of the last subject randomized in the study, or until death, or consent withdrawal. Public records may be used for contact information and/or to document date of death, as permitted by local law.

6.5. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal Section) section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression in the Intensive and Non-Intensive Chemotherapy Study or Treatment Failure or Hematologic relapse (Lack of Efficacy) in the Intensive Chemotherapy Study according to the 2017 ELN Recommendations (Appendix 4):[16]

- Global deterioration of health status requiring discontinuation;

- Unacceptable toxicity (of either study treatment);
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Subject refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Study terminated by Sponsor;
- Lost to follow-up;
- Withdrawal of subject consent for any further contact;
- Death.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status

(whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessments

Safety assessments will include collection of AEs, SAEs, vital signs, physical examinations, triplicate ECGs (12-lead), laboratory assessments (including genetics), transfusions, HSCT-related information, and verification of concurrent medications and interventions.

7.1.1. Cardiac Testing (MUGA/ECHO)

For subjects to be enrolled in the Intensive Study, an ECHO or MUGA scan is required at screening. If the LVEF is ≥50%, the subject may proceed to their first induction therapy. If the LVEF is <50%%, the subject may not be included in the Intensive Chemotherapy Study, per Section 4.2 and may be eligible for the treatment in the Non-intensive Chemotherapy Study.

If a second cycle of induction chemotherapy is indicated, a second MUGA or ECHO is required prior to initiating the second cycle if clinically indicated (eg, subject exhibiting signs of cardiac failure). If the second MUGA or ECHO demonstrates a LVEF <45%, the subject is not eligible to receive additional induction chemotherapy and will be removed from the trial.

7.1.2. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study treatment - once at the start of screening and once at the baseline visit andimmediately before investigational product administration (first dose). In addition, for the Intensive Study, a pregnancy test must also be done at the start of every Induction (1,2) during the active treatment period, and at Day 1 of each Consolidation Cycle with single-agent cytarabine, Day 1 of each cycle for single-agent glasdegib/placebo following the period labeled as "Consolidation up to 2 years post randomization" (as labeled in Table 1), and the end of treatment. For the Non-intensive Study, a pregnancy test must be done every cycle during the active treatment period and at the end of treatment.

Following a negative pregnancy result at screening, appropriate contraception (defined in Section 5.3) must be commenced and a further negative pregnancy result will then be required at the baseline visit before the subject may receive the study treatment. Pregnancy tests will be repeated at every treatment cycle or start of each induction(s) during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRBs)/Ethic Committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of study treatment and enter into the Follow-up phase of the study.

7.1.3. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness. Additional information regarding AE and Serious AE (SAE) reporting is provided in Section 8. Assessment of acute GVHD will be graded by standard criteria based on the Consensus Conference on acute GVHD Grading (Appendix 15).[46] Assessment of chronic GVHD will be assessed based on the National Institutes of Health (NIH) Diagnosis and Staging Working Group Report.[47,48]

7.1.4. Laboratory Safety Assessments

Hematology, blood chemistry, coagulation and urinalysis assessments will be drawn at the time points described in the Schedule of Activities and will be analyzed by the site/Investigator at local laboratories. Laboratory certifications and normal ranges with units must be provided to the Sponsor.

Laboratory assessments should be obtained during the 28-day screening period as described in the Schedule of Activities and as defined in Table 12. There is no need to repeat on Day 1 if these assessments are performed within 3 days prior to randomization. From Cycle 2 Day 1 (C2D1) onwards (or Induction 2 onward), if a hematology (complete blood count [CBC] with differentials) sample is obtained within 3 days of a scheduled blood draw, the collection need not be repeated. For those subjects achieving a CR or PR, a CBC should be done at least 4 weeks after the BM assessment in order to confirm response. Hematology tests may be repeated also as clinically indicated.

If blood chemistry or coagulations are obtained within 3 days of scheduled blood draw, the collection need not be repeated.

Urinalysis is required during the screening period, and may be repeaated on study as clinically indicated.

For laboratory evaluations used to determine eligibility, a repeated evaluation is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the subject will be considered a screening failure. Re-screening is allowed in this study.

See Table 12 for a list of required laboratory tests.

Table 12. Required Laboratory Tests

Hematology	Blood Chemistry	Urinalysis (microscopic analysis)	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT[2]		aPTT	For female subjects of childbearing potential, serum or urine
Platelets	AST[2]		INR	
WBC	Alkaline Phosphatase	Specific Gravity		
Absolute Neutrophils[1]	Sodium	PH		
Absolute Lymphocytes[1]	Potassium	Protein		
Absolute Monocytes[1]	Magnesium	Glucose		
Absolute Eosinophils[1]	Chloride	RBC		
Absolute Basophils[1]	Total Calcium	WBC		
Blast Count	Total Bilirubin[2]	Ketones		
	BUN or Urea	Leukocyte Esterase		
	Creatinine			
	Uric Acid			
	Glucose (non-fasting)	Nitrate		
	Albumin			
	Total Protein			
	Phosphorus			
	LDH			
	CPK			
	Bicarbonate[3]			

1 The database allows differential counts as both percent and absolute values for these analytes, the preference is absolute if both are available. If only percents are available, thee values may be entered.

2. For potential Hy's law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. AEs of Hy's law must be reported as an SAE. Refer to Section 8.4.2 for detailed instructions.

3. Required for Non-Intensive subjects, optional for Intensive subjects.

ALT= alanine aminotransferase, aPTT= activated partial thromboplastin time, AST= aspartate aminotransferase, BUN=blood urea nitrogen, CPK= creatinine phosphokinase, INR=international normalization ratio, LDH=lactate dehydrogenase, RBC=red blood cell count, U/A= urinalysis, WBC= white blood cell count.

7.1.5. Transfusions

All red blood cell and platelet transfusions, including the date of each transfusion and number of red blood cell or platelet units transfused must be recorded while the subject is on treatment in the **Intensive and Non-intensive studies**. Transfusion histories for the 8 weeks prior to randomization must also be recorded in the CRF **for the Non-intensive study only**. Note that the number of units (not the number of bags) must be recorded.

Transfusions will not be collected during the HSCT period (Day 1 of conditioning until resuming glasdegib or placebo, death, withdrawal, or post therapy follow up).

7.1.6. Vital Signs and Physical Examination

Vital signs will include blood pressure and heart rate (to be recorded in sitting position). Subjects will have a physical exam (PE) including an examination of major body systems, measurement by palpation of spleen and liver, weight, height and assessment of Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 3). If PE obtained within 48 hours of previous assessments, the evaluation need not be repeated. Height need not be recorded after the first measurement at screening. Weight must be recorded at Screening and Day 1 of each cycle or Day 1 of Induction(s).

7.1.7. Triplicate (12-Lead) ECGs

See the Schedule of Activities for the specific time points of local Electrocardiogram (ECG) collection and Table 10 for dose modifications related to management of QTcF prolongation.

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be performed for ECGs at every time point. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. The acceptable mean on treatment upper limit of QTc interval will be using the Fridericia (QTcF) correction method. At each time point 3 consecutive supine ECGs will be performed approximately 2 minutes (but no longer than 5 minutes) apart, to determine the mean QTcF interval. The sites will be provided with a simple calculation tool that will allow for real-time assessment of mean QTcF values from the triplicate QT and heart rate measurements.

The acceptable mean on-treatment upper limit of QTcF interval is 480 msec. If any subject has a mean pre- or post-dose QTcF value >480 msec, please refer to Table 10 of the protocol for detailed instructions on management of QTcF prolongation and handling dose delays and dose modifications for glasdegib/placebo.

When matched with PK sampling, every effort should be made to perform the ECGs before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). A 15-min window for each ECG collection is allowed around the nominal ECG time point.

7.1.8. HSCT-Related Information

Donor details, type of transplant (myeloablative, non-myeloablative, or reduced intensity), day of donor stem cell infusion, and conditioning regimen (including radiation) will be collected in the CRF. Presence of GVHD prior to resuming glasdegib/placebo post HSCT will be reported in the CRF. HSCT–related information must be made available to the B1371019 study staff and must be able to be monitored.

Post Remission HSCT period (HSCT period) is defined as time from start of conditioning until resuming glasdegib/placebo, death, withdrawal of consent, or entering follow up period post HSCT. No concomitant medications (including transfusions) will be collected during the HSCT period. Day 0 is defined as the day of stem cell infusion (HSCT).

Post HSCT, any ongoing AEs and concomitant medications to treat ongoing AEs from the HSCT period must be collected in the CRF.

7.1.9. ANC Engraftment

Following post remission HSCT, ANC engraftment must be confirmed before resuming glasdegib or placebo. Confirmed ANC engraftment is defined by ANC $\geq 0.5 \times 10^9$/L for 3 consecutive days without growth factor support following HSCT using myeloablative or non-myeloablative conditioning regimen.

7.1.10. Pharmacokinetics Assessments

Every effort must be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, PK samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection should be noted on the CRF. The pre-dose PK sample should be collected within 30 minutes prior to administration of the drug. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be rescheduled with agreement of clinical investigators, subject and sponsor.

PK samples will be assayed using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the laboratory manual.

7.1.10.1. Glasdegib

Blood samples (1.5 mL whole blood sufficient to provide a minimum of 0.6 mL of plasma) will be collected for PK analysis of glasdegib as outlined in the PK flowchart (see Table 2 and Table 4).

7.2. Efficacy Assessments

7.2.1. AML Response Criteria

Disease response, measured from baseline through the End of Treatment will be evaluated using a modified version of the European LeukemiaNet (ELN) recommendations for diagnosis and management of AML in adults (Appendix 4).[16] ELN response assessments include evaluation of bone marrow, peripheral blood neutrophils, platelets, and blast %, assessment for EMD, and results from central lab MRD assessment. Every subject must have an Investigator determined Response Assessment documented per Appendix 4 or response should be marked as indeterminate if the evaluation does not meet a specific ELN response criterion.

All subject files and bone marrow assessment slides/samples must be available for source verification.

CR with partial hematologic recovery (CRh) will be assessed for the Non-intensive chemotherapy study. CRh is defined as ANC $>0.5x10^9$/L and platelets $>50x10^9$/L without qualifying for CR.

7.2.2. Genetics

For all subjects, genetics must be performed using any scheduled or unscheduled bone marrow biopsy and/or aspirate samples collected during study participation.

Baseline genetics classification must be completed within 28 days of first dose. Genetic risk will be classified according to the the ELN recommendations for diagnosis and management of AML in adults (Appendix 14).[16]

Baseline genetics classification known at the time of randomization will be used to stratify subjects; therefore, the Investigator must review available, baseline genetic and molecular reports and stratify each subject.

Following baseline assessments, subsequent analysis of genetic abnormalities may be restricted to abnormalities identified at baseline. Molecular abnormalities will be repeated at each none marrow assessment per standard of care.

7.2.3. Bone Marrow Assessments

Please see the Schedule of Activities for specific assessment time points for BM biopsy and/or aspirate collection. Bone marrow samples should be prepared according to the study Laboratory Manual. Results of all bone marrow evaluations performed during the study participation will be reported in the CRF.

The importance of timely and complete disease assessments (including BM assessments) at screening and during the study cannot be understated. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and have the potential to weaken the conclusions of this study.

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The two samples that are collected for MRD analysis, the bone marrow aspirate sample and the whole blood sample should be collected as they are **not** exploratory research biomarker samples. Both of these samples for MRD analysis are part of the response assessments in the main study; therefore, these samples are a required part of the study and **should always be collected.** Following MRD analysis on the whole blood sample, any remaining sample will be discarded rather than being used for molecular profiling.

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7.4. Patient Reported Outcomes (PROs)

Patient reported outcomes will be assessed using the MD Anderson Symptom Inventory AML/MDS Module (MDASI-AML/MDS), EuroQol 5-Dimension questionnaire 5-Level version (EQ-5D-5L), Patient Global Impression of Symptoms (PGIS), and Patient Global Impression of Change (PGIC). CCI [redacted]

PROs are completed at the same interval as drug dosing, clinical visits, and post-treatment follow-up are conducted. Refer to Table 1 and Table 3 for specific timepoint requirements. PGIC is completed at all post baseline time points, without the initial baseline assessment. PRO responses will be obtained directly from patients while on treatment and during the first two years of post-treatment follow-up. During the long term follow up phase, PRO responses may betranscribed and entered by site staff. PROs should never be completed more than once on any calendar day. For subjects hospitalized or with a timepoint falling on a weekend or holiday, the PRO may be performed on the next business day.

Site staff role must be strictly limited to transcription and data entry of patient responses, without any attempt to interpret, lead, or influence. Interviewer administration may be used under special circumstances (eg, patient is visually impaired, forgot their glasses, or feels too ill). If interviewer administration is required, every effort should be made to have the same interviewer administer the PRO surveys to the patient. In addition, the interviewer will stay true to the patient's response and not alter it.

Patients must complete these PRO surveys prior to any discussion of the patient's health or treatment with their physician or other healthcare personnel at the site. While every effort should be made to have patients complete these PRO surveys prior to dosing with any study drugs and other clinical procedures, flexibility is allowed to accommodate for site-specific operating procedures.

The data entered into the device will be considered the source documents and sent electronically to the vendor when completed. Patient responses will be captured in a database and maintained by the vendor and transferred to the Pfizer database.

7.4.1. MDASI-AML/MDS

The MDASI-AML/MDS is a validated modulized patient reported outcome measure for AML and MDS.[49-51]

It consists of a 19-item core cancer module and a four-item AML/MDS specific module [Appendix 9]. The 23 items are designed to measure 13 core cancer symptoms (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, problem remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness), 4 AML/MDS-specific symptoms (malaise, diarrhea, muscle weakness, and skin problems), and 6 areas of interference (general activity, mood, work, walking, relations with other people, and enjoyment of life) The core module's 13 core symptoms and 6 core interference items, are found to have the highest frequency and/or severity in patients with various cancers and treatment types. The four-item AML/MDS-module includes additional symptoms that are uniquely relevant to patients with AML and MDS.

It measures at the severity of symptoms and related interference at their WORST level in the last 24 hours by asking patients to respond to each item on an 0-10 numeric rating scale (NRS), where 0 = "not present" or "did not interfere" and 10 = "as bad as you can imagine" or "interfered completely".

The instrument is brief, simple, and easy to use. Its 24 hour recall period and 0-10 numerical rating scale are easy for patients to understand and complete. The burden to the patient is minimal, as it takes a few minutes to complete the questionnaire.

For this study, the response for the single item "Fatigue" (one of the 13 MDASI core cancer symptoms) will be analyzed separately as the key secondary efficacy endpoint.

7.4.2. EQ-5D-5L

The EQ-5D-5L (Appendix 10) is a brief, self-administered, validated and reliable generic health status instrument developed by the EuroQoL Group. It consists of the EQ-5D descriptive system and a visual analogue scale (VAS), the EuroQoL visual analogue scale (EQ-VAS).

The EQ-5D descriptive system measures a patient's health state on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patient is asked to indicate his/her health state by rating each dimension on a five-level scale (1=no problem, 5=extreme problem). This rating resulted in a 1-digit number expressing the level selected for that dimension. The digits for the 5 dimensions were combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score.

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, can be converted into a single index value (the EQ-5D Index or "utility") between 0 to 1 by applying a formula that essentially attaches country-specific values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (ie, state 11111).

Currently, EQ-5D-5L value sets are available for each country that performed a valuation study for the EQ-5D-3L. By using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, index values for the EQ-5D-5L can be calculated. Documents containing tables of values for all 3125 health states and the 'EQ-5D-5L Crosswalk Index Value Calculator' can be downloaded from the EuroQol website.

The EQ-5D Index scores range generally from 0 to 1, with 0 representing the worst health state and 1 as perfect health. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions.

The EuroQoL visual analogue scale (EQ VAS) records the respondent's self-rated health on a 20-cm vertical, visual analogue scale from 0 (worst imaginable health state) to 100 (best imaginable health state). This information could then be used as a quantitative measure of health as judged by the individual respondents.

A score difference of 0.08 for the EQ-5D Index score and of 7 for the EQ-VAS are recommended as estimates of minimally important differences for the EQ-5D.

7.4.3. Patient Global Impression of Symptoms

The Patient Global Impression of Symptoms (PGIS) (Appendix 11) and the Patient Global Impression of Change (PGIC) (Appendix 12) are employed as anchors in responder analyses for MDASI-AML/MDS, especially the fatigue item, which is a key secondary endpoint. PGIS is generally the preferred anchor over PGIC because PGIC may be subject to recall bias. As recommended by the Food and Drug Administration (FDA), for this protocol, both anchor scales will be used to provide an accumulation of evidence to help interpret a clinically meaningful score change in MDASI-AML/MDS.

The PGIS (Appendix 11) is a single1-item questionnaire designed to assess patient's overall impression of disease severity at a given point in time. It uses a 4-point Likert scale as follows: In the last 24 hours, my leukemia symptoms are: 1-"Absent (no symptoms)", 2-"mild", 3-" moderate", 4="severe", .

It will be used as an anchor for defining a "responder threshold", on MDASI-AML/MDS and can also be used to create severity categorization for this PRO to enhance interpretation.

Patients complete this questionnaire at baseline, and repeatedly at the same time points as the MDASI-AML/MDS is collected.

7.4.4. Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) (Appendix 12) is a single-item questionnaire designed to assess the patient's overall sense of whether there has been a change since starting treatment as rated on a 7 point Likert scale anchored by (1) 'very much improved' to (7) 'very much worse', with (4) =' no change'. The PGIC is a measure of "participant rating of global improvement and satisfaction with treatment".

1. This instrument is used to determine global improvement as assessed by the patient and as an anchor to define a responder definition for MDASI-AML/MDS and as a sensitivity analysis for defining a 'clinical important difference' on this PRO.

2. Patients complete this questionnaire repeatedly at the same post baseline time points as the MDASI-AML/MDS.

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8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Table 13. Adverse Event Reporting

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
HSCT Day 0 until resume study therapy, death, withdrawal or post-treatment follow up: All deaths, Grade 3/Grade 4 treatment-related AEs, and treatment related SAEs	Related to glasdegib or placebo and deaths regardless of causality[a]	Serious and related to glasdegib or placebo and deaths regardless of causality
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)
Note: Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor. a. In Germany only: All SAEs, regardless of causality, will be recorded on the CRF.		

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Subjects must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, (ie, prior to undergoing any study related procedure and/or receiving investigational product), through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.

- The HSCT Post Remission Period (HSCT Period) is defined as time from the start of the conditioning regimen until the subject restarts glasdegib or placebo, death, post study follow up, or withdrawal. For subjects being treated with HSCT, subjects must be followed for AEs for at least 28 days after the last investigational treatment administration prior to HSCT. Following HSCT Day 0, all deaths regardless of causality, Grade 3/Grade 4 treatment-related AEs, and SAE events that the investigator believes have at least a reasonable possibility of being related to study drug during the HSCT period are to be reported to the sponsor. In Germany only: All SAEs, regardless of causality, will be recorded on the CRF.

- Once subjects resume glasdegib or placebo following HSCT, events summarized in Table 13 will be reported.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a subject begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a subject begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

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8.3. Severity Assessment

AEs will be reported using concise medical terminology (verbatim) as well as the Common Terminology Criteria (CTC) term for Adverse Events (Version 4.03, Publish Date: June 14, 2010, http://ctep.cancer.gov/reporting/ctc.html)) listed in the Cancer Therapy Evaluation Program.

The investigator may use the following definitions of Severity in accordance with CTCAE Version 4.03 to describe the maximum intensity of the adverse event:

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

All cases of Grade >2 mQTcF prolongation regardless of causality and treatment arm must be reported as an SAE for up to 28 calendar days after the last dose of study drug administered. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller);

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an

anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information

regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

- If the dose administered is >120% of the scheduled dose, <80% of the scheduled dose, or dosed outside a 28 day window. If the drug is administered as incorrect formulation (ie, pills cut in half instead of administering a lower dosage tablet, pills crushed and administered via feeding tube without direction from Sponsor).

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Medication errors will NOT include:

- Cases where commercial backbone drug was used instead of supplied stock;
- Cases where the wrong lot number of drug was dispensed;
- Dose modifications outlined in Section 5.5.5.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

For the intensive chemotherapy population, a total of 267 death events will be required to provide 90% power to detect an HR=0.67 (translating in median OS of 31.5 vs 21 months, assuming a composite median OS of 21 months for intensive AML subjects: young intensive (aged ≤60 years) with a median OS of 23.7 months and elderly intensive (aged >60 years) with a median OS of 15 months[17,18] using a 1-sided log-rank test at a significance level of 0.025 and a 3-look group sequential design. A first interim analysis for efficacy and futility is planned when 50% of death events have occurred. However, no efficacy stopping will be made even if the endpoint crosses the efficacy boundary. A second interim analysis for efficacy and futility is planned when 70% of death events have occurred or upon completion of enrollment of intensive chemotherapy subjects, whichever is later. An O'Brien-Fleming boundary with Lan-DeMets spending function will be used for efficacy and a Rho(3) β-spending function will be used for the non-binding futility boundary. Assuming a

10-month ramp-up of subject enrollment up to 18 subjects per month then plateauing at that level and expecting approximately one third of all enrolled subjects to be censored, the desired number of death events will accrue within 58 months after randomization of the first intensive chemotherapy subjects with a total of 400 intensive chemotherapy subjects using a 1:1 randomization. The actual time needed to accrue the desired number of events will be impacted by actual subject enrollment and drop-out rates.

For the non-intensive chemotherapy population, a total of 220 death events will be required to provide 90% power to detect an HR=0.64 (translating in median OS of 16.2 vs 10.4 months[9] using a 1-sided log-rank test at a significance level of 0.025 and a 2-look group sequential design. An interim analysis for efficacy and futility is planned when 60% of death events have occurred or upon completion of enrollment of non-intensive chemotherapy subjects, whichever is later. An O'Brien-Fleming boundary with Lan-DeMets spending function will be used for efficacy and a Rho(3) β-spending function will be used for the non-binding futility boundary. Assuming a 10-month ramp-up of subject enrollment up to 18 subjects per month then plateauing at that level and expecting approximately 31% of all enrolled subjects to be censored, the desired number of death events will accrue within 37 months after randomization of the first non-intensive chemotherapy subjects with a total of 320 non-intensive chemotherapy subjects using a 1:1 randomization. The actual time needed to accrue the desired number of events will be impacted by actual subject enrollment and drop-out rates.

9.2. Analysis Population

The primary, secondary, CCI analyses of intensive and non-intensive chemotherapy subjects will be conducted separately and independently of each other.

9.2.1. Full Analysis Set

The Full Analysis set (FAS) will include all randomized subjects. Subjects will be classified according to the treatment assigned at randomization.

9.2.2. Safety Analysis Set

The safety analysis set will include all subjects who receive at least one dose of study drug. Subjects will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case subjects will be classified according to the first study treatment received.

9.2.3. PK Analysis Set

The PK concentration analysis set is defined as all subjects who are treated and who have at least 1 value of analyte concentration of glasdegib available. The PK parameter analysis set is defined as all subjects who are treated and who have at least 1 of the PK parameters of interest.

CCI [redacted]

9.3. Efficacy Analysis

9.3.1. Analysis of the Primary Endpoint

OS is defined as the time from the date of randomization to the date of death due to any cause. Subjects last known to be alive will be censored at date of last contact.

For the intensive chemotherapy population, the primary analysis of OS will be performed based on the FAS when about 267 death events have occurred in the intensive chemotherapy population. A 1-sided stratified log-rank test (stratified by ELN genetic risk, ≤60 vs >60 years, and region [rest of world {ROW} vs China]) will be used at the interim and final analyses with the overall significance level preserved at 1-sided ≤0.025. The rate of stem cell transplantation is expected to be much lower for sites in China versus the ROW thus region is being added as a stratification factor in the primary analysis. Should over-stratification prevent model convergence or there exists large imbalance in the distribution (eg, 90% or more subjects from one strata level), the intermediate and poor cytogenetic risk groups may be pooled in the analysis. OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate CIs for the 25th, 50th (median), and 75th percentiles of OS will be reported using Brookmeyer and Crowley method.[45] In addition, the median OS and its two-sided 95% CI using the same method will be provided for each stratum within each treatment arm separately. The Cox proportional hazards model will be fitted to compute the treatment HR and the corresponding 95% CI. The HR and its two-sided 95% CI will be provided for each stratum as well. Additional covariates may be added in the Cox proportional hazard model to explore the potential influence of other baseline factors on OS (including but not limited to age, race, gender, and secondary AML). CCI [redacted] The Schoenfeld residuals for the stratified Cox PH regression model will be plotted to investigate graphically violations from the PH assumption; a non-zero slope is evidence of departure from PH. The PH assumption will be formally tested using Schoenfeld's residual test. Large departures from PH will be evidenced by a p-value <0.05. CCI [redacted]

For the non-intensive chemotherapy population, the primary analysis of OS will be performed based on the FAS when about 220 death events have occurred in the non-intensive chemotherapy population. A 1-sided stratified log-rank test (stratified by ELN cytogenetic risk and age <75 vs ≥75 years) will be used at the interim and final analyses with the overall significance level preserved at 1-sided ≤0.025. The rate of stem cell transplantation is expected to be low in all regions in the non-intensive study. Should over-stratification

prevent model convergence or there exists large imbalance in the distribution (eg, 90% or more subjects from one strata level), the intermediate and poor genetic risk groups may be pooled in the analysis. OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th (median), and 75th percentiles of OS will be reported using Brookmeye and Crowley method.[45] In addition, the median OS and its two-sided 95% CI using the same method will be provided for each stratum within each treatment arm separately. The Cox proportional hazards model will be fitted to compute the treatment HRs and the corresponding 95% CI. The HR and its 2-sided 95% CI will be provided for each stratum as well. Additional covariates may be added in the Cox proportional hazard model to explore the potential influence of other baseline factors on OS (including but not limited to age, race, gender, and ECOG performance status). CCI [redacted] The Schoenfeld residuals for the stratified Cox PH regression model will be plotted to investigate graphically violations from the PH assumption; a non-zero slope is evidence of departure from PH. The PH assumption will be formally tested using Schoenfeld's residual test. Large departures from PH will be evidenced by a p-value <0.05. CCI [redacted]

[redacted]

9.3.2. Analysis of Secondary Endpoints

All secondary PRO and efficacy endpoints will be based on the FAS unless stated otherwise.

Fatigue

The key secondary PRO endpoint based on the Fatigue single-item from the MDASI-AML/MDS questionnaire will be analyzed for proportion of responders (defined below) at week 12 for non-intensive patients and week 8 for intensive chemotherapy patients. The proportion of responders will be estimated with a 2-sided 95% CI (using normal approximation). The proportion and 2-sided 95% CI (using exact method) of responders for each stratum will also be provided. A hierarchical testing procedure will be followed, namely, a formal testing of proportion of responders (using a 1-sided Cochran Mantel Haenszel [CMH] test, stratified by ELN genetic risk, age [age ≤60 vs >60 years for the intensive patients, and age <75 vs ≥75 years for the non-intensive patients]), and region [ROW vs China for intensive patients only]) will only be conducted in one population if the primary OS endpoint is met in that population (intensive or non-intensive treatment). The risk ratio and 2-sided 95% CI will also be summarized.

Responder definition will be determined via anchor-based methods using PGIS (primary) and PGIC (supportive), which will be supplemented with cumulative distribution functions (CDF) and probability density functions (PDF). Detailed description of the methodology will be in the statistical analysis plan.

CDF and PDF will be created using individual change from baseline for the fatigue item score from the MDASI-AML/MDS at week 8 for intensive chemotherapy patients and at week 12 for non-intensive patients.

Disease Specific Efficacy Endpoints

Disease specific efficacy endpoints include CR, CR_{MRD^-neg} (a subgroup of CR), Complete remission with incomplete hematologic recovery (CR_i), Complete remission with partial hematologic recovery (CRh, only defined for Non-intensive patients), Morphological Leukemia Free State (MLFS), and Partial Remission, as defined according to the 2017 ELN recommendations.[16] Note that CR (including CR_{MRD^-neg}) is always a deeper response than CRi. CR (including CR_{MRD^-neg}) is a deeper response than CRh (if applicable), and CRh (if applicable) is a deeper response than CRi.

The proportion of subjects achieving each endpoint will be estimated with 2-sided 95% CI (using the normal approximation) respectively. The proportion and 2-sided 95% CI of subjects achieving each of the endpoint for each stratum will also be provided. The proportion of subjects achieving each endpoint will be compared between the treatment arms using a 1-sided CMH stratified test (stratified as described in Section 9.3.1) and an unstratified chi-square test.

Duration of Response

For the Intensive chemotherapy subjects, Duration of Response (DoRi) is only defined for subjects who have ever achieved CRi or better on study as the time from date of first achieving CRi or better to the date of disease progression, or relapse after CRi or better, or death due to any cause. Subjects last known to be alive who are free from disease progression or relapse after CRi or better are censored at the date of last disease assessment that verifies their status. Note that CRi or better includes CR and CRi for the intensive chemotherapy subjects.

For non-Intensive chemotherapy subjects, DoRi is only defined for subjects who have ever achieved CRi or better on study as the time from date of first achieving CRi or better to the date of disease progression, or relapse after CRi or better, or death due to any cause. We also define DoRh for subjects who have ever achieved CRh or better on study as the time from date of first achieving CRh or better to the date of disease progression, or relapse after CRh or better, or death due to any cause. Note that CRi or better includes CR, CRh, and CRi for the non-intensive chemotherapy subjects. CRh or better includes only CR and CRh for the same subjects.

As DoRi/DoRh are not defined for all subjects, no formal statistical comparison will be made between treatment arms. DoRi/DoRh will be analyzed and displayed graphically for each arm separately using the Kaplan-Meier method. The median DoRi/DoRh for each treatment arm and corresponding two-sided 95% CI will be provided.

Time to Response (Non-Intensive Study only)

Time to Response (TTRi) is only defined for subjects who have ever achieved CRi or better on study as the time from date of randomization to date of first achieving CRi or better. Similarly, TTRh is only defined for subjects who have ever achieved CRh or better on study as the time from date of randomization to date of first achieving CRh or better.

As TTRi/TTRh are not defined for all subjects, no formal statistical comparison will be made between treatment arms. The minimum, median, and maximum TTRi/TTRh for each treatment arm will be provided.

Event Free Survival

Intensive Study

For the Intensive chemotherapy patients, EFS is defined as the time from the date of randomization to the date of treatment failure (TF), relapse from CR, or death from any cause, whichever comes first. TF is defined as failure to achieve CR during the induction cycle (including the re-induction cycle if there is one) and the event date for TF is the day of randomization. Responders last known to be alive who are free from disease progression or relapse are censored at the date of last disease assessment that verifies their status.

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Non-intensive Study

For Non-intensive chemotherapy patients, EFS is defined as the time from the date of randomization to the date of TF, relapse from CRh or better, or death from any cause, whichever comes first. TF is defined as failure to achieve CRh or better following up to 6 cycles of study treatment and the event date for TF is the day of randomization. Patients who discontinue either study treatment without achieving CRh or better prior to completing 6 cycles of study treatment are considered treatment failures. Responders last known to be alive who are free from disease progression or relapse are censored at the date of last disease assessment that verifies their status.

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- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

A 1-sided stratified log-rank test (stratified by ELN genetic risk, age [age ≤60 vs >60 years for the intensive patients, and age <75 vs ≥75 years for the non-intensive patients], and region [ROW vs China for intensive patients only]) will be used. Should over-stratification prevent model convergence or there exists large imbalance in the distribution (eg, 90% or more subjects from one strata level), the intermediate and poor cytogenetic risk groups may be pooled in the analysis. EFS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate CIs for the 25th, 50th, and 75th percentiles of EFS probabilities will be reported (using Brookmeyer and Crowley method).[44] In addition, the median EFS and its two-sided 95% CI using the Brookmeyer and Crowley method[45] will be provided for each stratum within each treatment arm separately. The Cox proportional hazards model will be fitted to compute the treatment HR and the corresponding 95% CI. The HR and its two-sided 95% CI will be provided for each stratum as well.

Patient Reported Outcomes

Analysis of patient-reported outcomes will be based on the MDASI-AML/MDS, EQ-5D-5L, PGIS, PGIC, CCI [redacted] For MDASI-AML/MDS and EQ-5D-5L, a completion table will be constructed showing the number and percentage of subjects at each time point for each treatment group by each domain. Analysis of MDASI-AML/MDS and EQ-5D-5L will be based on their respective subscales as defined in the guidance document for each of these instruments.

Particularly, although fatigue is the most commonly experienced symptom among AML patients, other symptoms also may be relevant for patients. Accordingly, analysis of MDASI-AML/MDS will be based on the core cancer symptom score, the AML/MDS-specific symptom score, the interference areas score, and also the 5 individual items of fatigue, disturbed sleep, dry mouth, muscle weakness, and lack of appetite. Note that Fatigue also appears earlier in Section 9.3.2 (as a key secondary endpoint) using a responder analysis.

A display of descriptive statistics including means, medians, standard deviations, and 95% confidence intervals at each assessment point will be provided. This will be done based on the observed values as well as on change from baseline values. Statistical comparison of the 2 treatment groups will be based on a longitudinal repeated measures mixed effects model using baseline as a covariate.

CCI [redacted]

Pharmacokinetic Analysis

PK Parameters:

For intensive and non-intensive studies, the plasma trough concentration (C_{trough}) will be reported for glasdegib (and metabolite, if relevant). Descriptive statistics will be provided for these PK parameters in tabular form (n, mean, standard deviation (Stdev), CV, median, minimum, maximum, geometric mean and its associated CV) by cycle (or induction 1,2) and day.

PK Concentrations:

For drug concentrations, individual values and descriptive statistics (n, mean, Stdev, CV, median, minimum, maximum, geometric mean and its associated CV) will be presented by cycle (or induction 1, 2), day of assessment, and nominal time in tabular form.

Population Pharmacokinetic Analysis or PK/PDx Modeling

PK and pharmacodynamics (PDx) data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any causal relationship between study treatment exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

CCI [redacted]

CCI

[redacted]

[redacted]

9.5. Safety Analysis

9.5.1. Adverse Events

All subjects who receive any study treatment (safety analysis set) will be included in the summaries and listings of safety data. Overall safety profile and tolerability of the glasdegib + other study treatment and the placebo + other study treatment arm will be characterized by type, frequency, severity, timing, and relationship to study therapy of adverse events and laboratory abnormalities.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

In all summaries, emphasis will be placed on treatment emergent adverse events (TEAEs). Adverse events will be summarized by the frequency of subjects experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE (version 4.03) grade. Summaries will also be provided of treatment related TEAEs, namely, those judged by the investigator to be related or likely related to study drug.

Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE version 4.03 Grade 3 or higher, study drug related events, and serious adverse events will be considered with special attention. Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9.5.2. Laboratory Test Abnormalities

The number and percentage of subjects who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay, graded according to NCI CTCAE version 4.03. The analyses will summarize laboratory tests both on the entire study period and by cycle and/or Induction (Cycle 1 and Cycles beyond 1 or Induction 1,2). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTC grade definitions, results will be categorized as normal, abnormal or not done.

9.5.3. Baseline Characteristics

Subject characteristics at the time of study entry will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables for the full analysis set (see Section 9.2.1 for definitions of study populations). Imbalances in subject characteristics in the treated populations will be assessed.

9.5.4. Electrocardiogram Analysis

The QT measurements corrected by heart rate (QTc) will be used for the data analysis and interpretation. QTcF is planned to be the primary analysis method for the QTc endpoint. In addition a study-specific correction method (QTcS) and QTcB may also be evaluated for the QTc evaluable subjects. The most appropriate correction method that eliminates any QT vs. RR relationship may be chosen after review of the data.

9.5.4.1. Summary and Categorical Analysis of Electrocardiogram Findings

The analysis of ECG results will be based on subjects with both baseline and on-treatment ECG data. All ECGs obtained during the study will be evaluated for safety. ECG collected prior to the first day of dosing will be considered the baseline ECG.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis as individual values obtained at unscheduled time points.

Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF and QTcB. Individual QTc (all evaluated corrections) intervals will be listed by time. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment, and by treatment and time point. For each subject by treatment the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Outlier analysis of the QTc data will be conducted and summarized as follows:

- The number of subjects with maximum change from baseline in QTc (<30, 30-<60, and ≥60 msec);
- The number of subjects with maximum post-dose (post-baseline) QTc (≤450, >450-≤480, >480- ≤500, and >500 msec);
- PR changes from baseline ≥25% and absolute values >200 msec;
- QRS changes from baseline ≥25% and absolute values >110 msec;
- Number and percentage of individuals with abnormal ECG findings.

Shift tables will be provided for baseline versus worst on study QTc (one or more correction method will be used). Tables of ECG abnormality at baseline (yes, no, not done: (n, %)) will also be provided. Subjects experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

9.6. Interim Analyses

The interim analyses will be performed based on the FAS for the intensive and non-intensive chemotherapy population separately and independently of each other.

For the intensive chemotherapy population, two interim analyses are planned. One efficacy and futility interim analysis is planned when 50% of death events have occurred in the intensive chemotherapy population. However, no efficacy stopping will be made even if the endpoint crosses the efficacy boundary. A second interim analysis of efficacy and futility is planned when 70% of death events have occurred or upon completion of enrollment of the intensive chemotherapy population, whichever is later. An O'Brien-Fleming boundary with Lan-DeMets spending function will be used for efficacy and a Rho(3) β-spending function will be used for the non-binding futility boundary. If exactly 50% of the events is accrued at the first interim analysis, the futility boundary will be crossed when 1-sided $p>0.461$. If exactly 70% of the events is accrued at the second interim analysis, the futility boundary will be crossed when 1-sided $p>0.186$ and the efficacy boundary will be crossed when 1-sided $p<0.007$. If the actual number of events at the interim analyses is different, the corresponding spending function will be used to calculate the actual stopping boundaries.

For the non-intensive chemotherapy population, one interim analysis is planned. An interim analysis of efficacy and futility is planned when 60% of death events have occurred or upon completion of enrollment of the non-intensive chemotherapy population, whichever is later. An O'Brien-Fleming boundary with Lan-DeMets spending function will be used for efficacy and a Rho(3) β-spending function will be used for the non-binding futility boundary. If exactly 60% of the events is accrued at the interim analysis, the futility boundary will be crossed when 1-sided $p>0.302$ and the efficacy boundary will be crossed when 1-sided $p<0.004$. If the actual number of events at the interim analyses is different, the corresponding spending function will be used to calculate the actual stopping boundaries.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC). The study team will remain blinded. An unblinded reporting team (separate from the study team) will work with E-DMC for the on-going monitoring.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. An E-DMC will be convened to monitor safety in the study at least once yearly. The E-DMC will also evaluate the results of all interim analyses.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects’ personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH Good Clinical Practice (GCP), local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of Study in all other participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of glasdegib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 14 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

After the end of the trial, the continuation of treatment; such as in an extension study, for those patients who are still receiving benefit in the non-intensive study may be decided based upon availability of alternative treatment options. An extension study **would not be available** for patients who receive HSCT within the non-intensive study. Non-intensive study subjects who receive HSCT would continue blinded therapy for up to 2 years post randomization, upon PD, relapse, consent withdrawal, or upon conversion to MRD-negative disease at 2 consecutive timepoints; whichever comes first.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in subjects) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual subjects has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
AHD	antecedent haematologc disease
ALT	alanine aminotransferase
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myelogenous Leukemia
ANC	absolute neutrophil count
APL	Acute Promyelocytic Leukemia
Ara-C	Cytarabine
ASCO	American Society for Clinical Oncology
CCI [redacted]	
AST	aspartate aminotransferase
ATRA	all-trans retinoic acid
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 to infinity
AZA	azacitidine
CCI [redacted]	
BCR-ABL1	BCR-ABL breakpoint cluster region-Abelson 1
BID	twice a day
BM	bone marrow
BSA	body surface area
BST	best supportive therapy
Ca	calcium
$C_{avg\ ss}$	steady state average concentration
CALGB	Cancer and Leukemia Group B
CBC	complete blood count
C#D#	Cycle # Day #
CD	cluster of differentiation
CDF	cumulative distribution functions
CI	confidence interval
CID	clinically important difference
CK	creatine kinase
C_{max}	maximum plasma concentration
CMH	Cochran Mantel Haenszel
CMML	Chronic myelomonocytic leukemia
CNS	central nervous system
CR	complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery

Abbreviation	Term
$CR_{MRD-neg}$	complete remission with negative minimal residual disease
CRF	case report form
CSA	clinical study agreement
CT	clinical trial
CTC	common terminology criteria
CTCAE	common terminology criteria for adverse events
C_{trough}	plasma trough concentration
CV	coefficient of variation
DDI	Drug-drug interaction
DILI	drug-induced liver injury
DLT	dose limiting toxicity
CCI [redacted]	
DoR	duration of response
DoRi	duration of response (response is defined as CRi or better)
DoRh	duration of response (response is defined as CRh or better)
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EFS	event-free survival
ELN	European Leukemia Net
EQ-VAS	EQ-5D visual analogue scale
EU	European Union
EudraCT	European Clinical Trials Database
EQ-5D-5L	EuroQol 5-Dimension questionnaire 5-Level version
FAS	full analysis set
FDA	Food and Drug Administration
FIP	first-in-participant
FLT3-ITD	fms-like tyrosine kinase internal tandem duplication
FSH	follicle-stimulating hormone
fu	fraction unbound
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GLI	glioma-associated oncogene homolog 1
GLP	good laboratory practice
GM-CSF	granulocyte-macrophage colony stimulating factor
GVHD	graft-versus-host disease
hCG	human chorionic gonadotropin

Abbreviation	Term
HDPE	high density polyethylene
HGRAC	Human Genetics Resources Administration of China
Hh	hedgehog
HIDAC	high dose Ara-C
HIV	human immunodeficiency virus
HR	Hazard ratio
HRQL	health-related quality of life
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ID	identification
IIR	investigator-initiated research
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IVR	interactive Voice Response
IWR	interactive web response
JAK	janus kinase
K	potassium
CCI	[redacted]
LDAC	low-dose cytarabine
LFT	liver function test
LIC	lead-in cohort
LSC	leukemia stem cells
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
MD	medical doctor
MDASI	MD Anderson Symptom Inventory
MDR-1	multi-drug resistance-1
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
Mg	magnesium
MLFS	morphologic leukemia-free state
MnB	meningitidis serogroup B
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition scan

Abbreviation	Term
mCR	marrow complete remission
mOS	median overall survival
n	number
NCI	National Cancer Institute
NIH	National Institutes of Health
N/A	not applicable
NOAEL	no observed adverse effect level
NPM1	nucleophosmin 1
NRS	numeric rating scale
OS	overall survival
PCD	primary completion date
PD	progressive disease
PDx	pharmacodynamics(s)
PE	physical examination
PEG	pegylated
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Symptoms
P-gp	p-glycoprotein
PGx	pharmacogenomics(s)
PH	potential of hydrogen
PK	pharmacokinetic
PML-RARA	Promyelocytic leukemia – retinoic acid receptor alpha
PO	by mouth, orally
PR	partial remission
PRO	patient reported outcomes
CCI [redacted]	
PT	prothrombin time
PTCH	patched
QALY	quality-adjusted life years
QD	once a day
QTc	QT interval corrected for rate
QTcF	QT interval corrected by the Fridericia Correction Formula
R_{ac}	accumulation ratio
RMST	restricted mean survival time
RNA	ribonucleic acid
ROW	rest of world
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCT	stem cell transplant
SD	stable disease

Abbreviation	Term
SMO	smoothened
SoA	schedule of activities
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
Stdev	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TdP	torsades de pointes
TEAE	treatment emergent adverse events
TESAE	treatment emergent serious adverse events
CCI	[redacted]
TF	treatment failure
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum plasma concentration
TTR	time to response
TTRi	time to response (response is defined as CRi or better)
TTRh	time to response (response is defined as CRh or better)
U/A	urinalysis
ULN	upper limit of normal
US	United States
UVB	ultraviolet B light
Vz/F	Apparent volume of distribution
WHO	World Health Organization

Appendix 2. 2016 WHO Classification of Myeloid Neoplams and Acute Leukemia

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood

Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Arber DA, Orazi A, Robert, H, et.al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016; 127 (20): 2391-2405.

Appendix 3. Eastern Cooperative Oncology Group Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.
By the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 4. Summary of Response Criteria and Progression Definitions for AML Treated with Intensive and Non-Intensive Chemotherapy used in BRIGHT AML1019

Response Criteria[1]	Minimal residual disease[1] (per central lab report only)	Peripheral Blood			Bone Marrow Blasts (%)	Other
		Neutrophils	Platelets	Peripheral Blasts (%)		
Treatment Response						
Complete Remission without minimal residual disease (CRMRD-)	MRD Negative	≥1 x 10^9 /L (≥1000µL)	≥100 x 10^9/L (≥100 000µL)	0	<5	
Complete Remission (CR)	MRD positive or unknown	≥1 x 10^9 /L (≥1000µL)	≥100 x 10^9/L (≥100 000µL)	0	<5	• Absence of extramedullary disease. • Absence of blasts with Auer rods.
Complete Remission with partial hematologic recovery (CRh)[2] APPLIES ONLY FOR THE NON-INTENSIVE STUDY	MRD positive or unknown	≥0.5 x 10^9/L (500µL)	≥50 x 10^9/L (≥50 000µL)	0	<5	• Assess in non-intensive chemotherapy study **only**, not qualifying for CR, ie, both neutrophil ≥0.5 x 10^9/L **and** platelets ≥50 x 10^9/L must be met, but does not satisfy both Neutrophils ≥1 x 10^9/L **and** Platelets ≥100 x 10^9/L at the same time. • Absence of extramedullary disease. • Absence of blasts with Auer rods.
Complete Remission with incomplete hematologic recovery (CRi)	MRD positive or unknown	< 1 x 10^9/L (<1000µL)	<100 x 10^9/L (<100 000µL)	0	<5	• Not qualifying for CR or CRh (if applicable), ie, • For intensive chemotherapy study: either neutropenia (<1 x 10^9 /L) **or** platelets (<100 x 10^9 /L) must be met. • For non-intensive chemotherapy study, either neutrophil <0.5 x 10^9/L **or** platelets <50 x 10^9/L) must be met. • Absence of extramedullary disease. • Absence of blasts with Auer rods.
Morphologic leukemia-free state (MLFS)	MRD positive or unknown				< 5	• Absence of extramedullary disease. • Absence of blasts with Auer rods. • No hematologic recovery required; marrow should not be aplastic; at least 200 cells enumerated or cellularity ≥10%.
Partial Remission	MRD	≥1 x 10^9/L	≥100 x 10^9/L	0	Decrease to	

(PR)	positive or unknown	(≥1000µL)	(<100 000µL)		5 – 25% AND Decrease of pre treatment bone marrow blast percentage by at least 50%.	
Response criteria for clinical trials						
Stable Disease (SD)	• Absence of CRMRD-, CR, CRh (if applicable), CRi, PR, MLFS, and criteria for PD not met. • Period of stable disease should be at least 3 months in the non-intensive only. The 3 month criteria does not apply to the intensive study.					
Progressive Disease (PD)	• Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in blood: • >50% increase over baseline (a minimum 15% point increase in cases with <30% blasts at baseline); or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5x10^9/L [500/µL], and/or platelet count to >50x10^9/L [50 000/µL] non-transfused); OR • >50% increase in peripheral blasts (WBC x %blasts) to >25x10^9/L (>25 000/µL) OR New extramedullary disease.					
Indeterminate	A response that does not fit the criteria for SD or PD. For example, when peripheral blood blast count assessed and no bone marrow assessment, or when a technical issue prevents the ability to make a response assessment (ie dry tap or insufficient sample), or when an SD is not maintained for 3 months in the non-intensive study.					
Other Responses referenced in ELN 2017[3]						
Relapse						
Hematologic relapse (after CRMRD-, CR, CRi)	Reappearance of blasts in peripheral blood; OR ≥5% bone marrow blasts; OR Development of extramedullary disease.					
Molecular Relapse (after CRMRD-)	Reoccurrence of MRD positive status.					
Treatment Failure						
Primary refractory disease	For Intensive study: No CR or CRi after 2 courses of induction treatment; excluding patients with death in aplasia or death due to indeterminate cause. For Non-Intensive study: failure to achieve CR or CRh following up to 6 cycles of study treatment, excluding patients with death in aplasia or death due to indeterminate cause.					
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia.					
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available.					

1. This study uses modified 2017 ELN recommendations. The definitions used in this study are shown in this table. Original ELN recommendations are found in: Dohner H, Etstey E, Grimwade D, et.al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017; 129 (4): 424-447.
2. CRh is not part of the 2017 ELN recommendations, but is a required assessment for the non-intensive chemotherapy study.
3. 2017 ELN recommendations are found in: Dohner H, Etstey E, Grimwade D, et.al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017; 129 (4):424-447.

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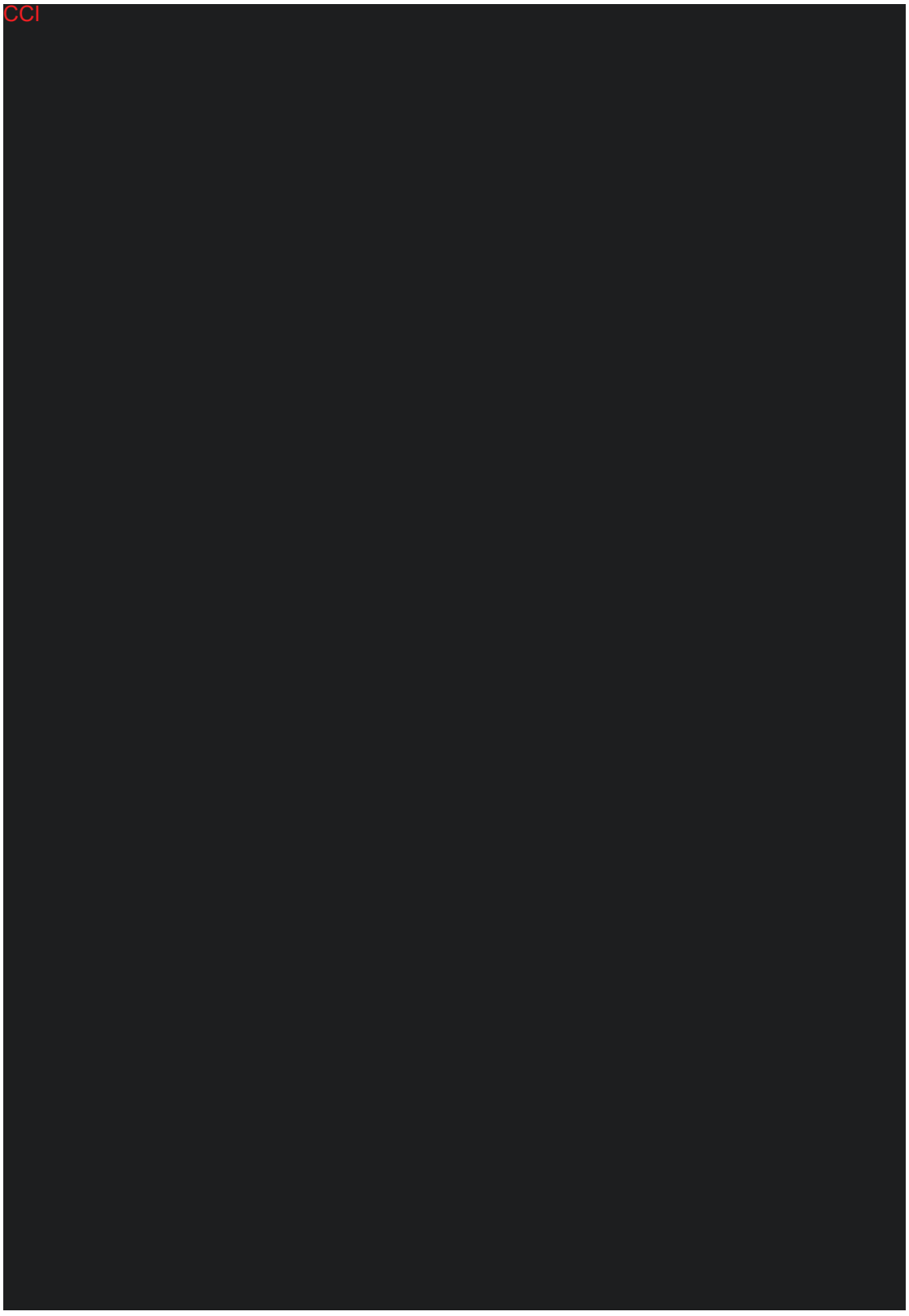

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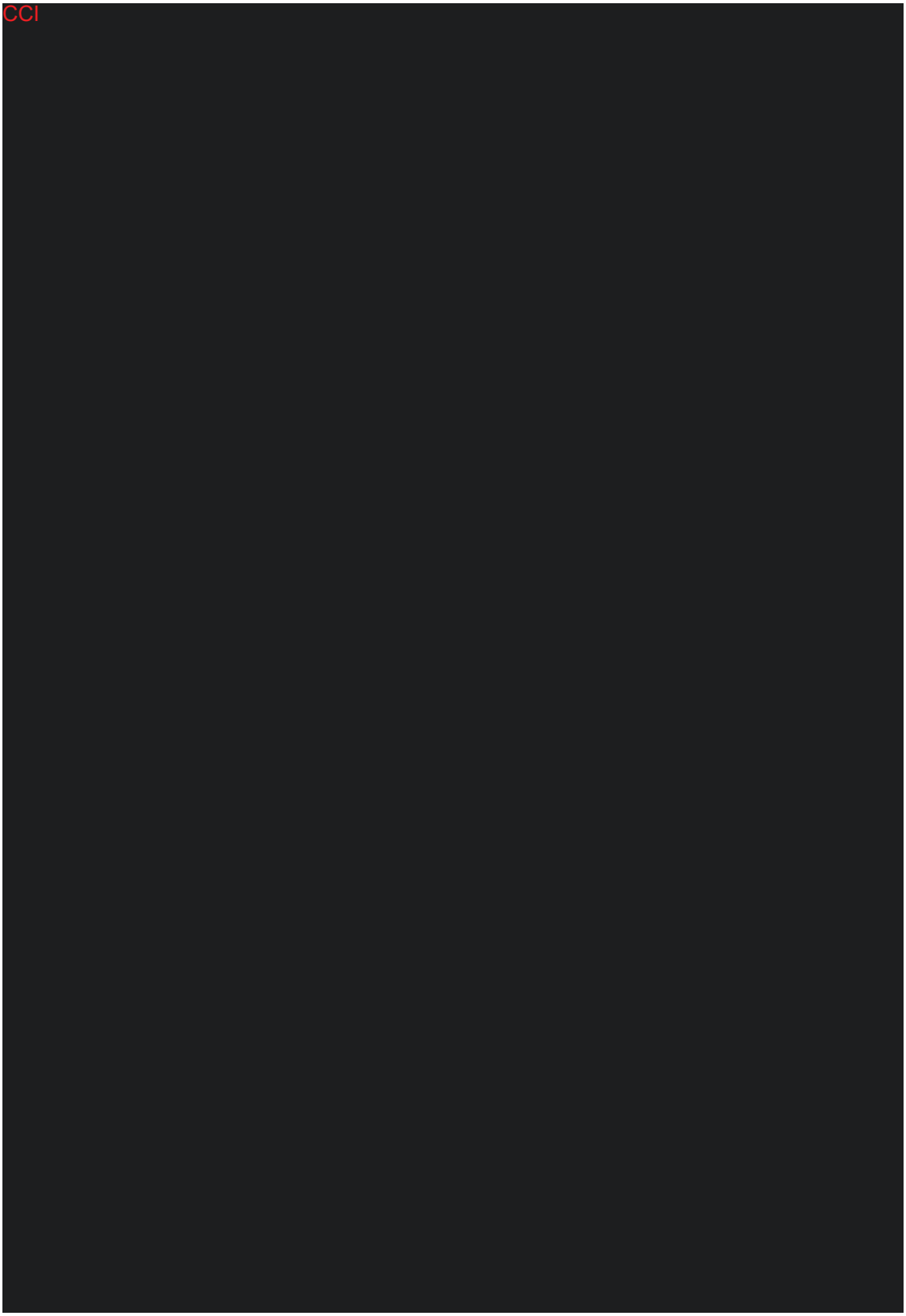

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Appendix 8. List of Drugs with Known Risk of Torsade de Pointes

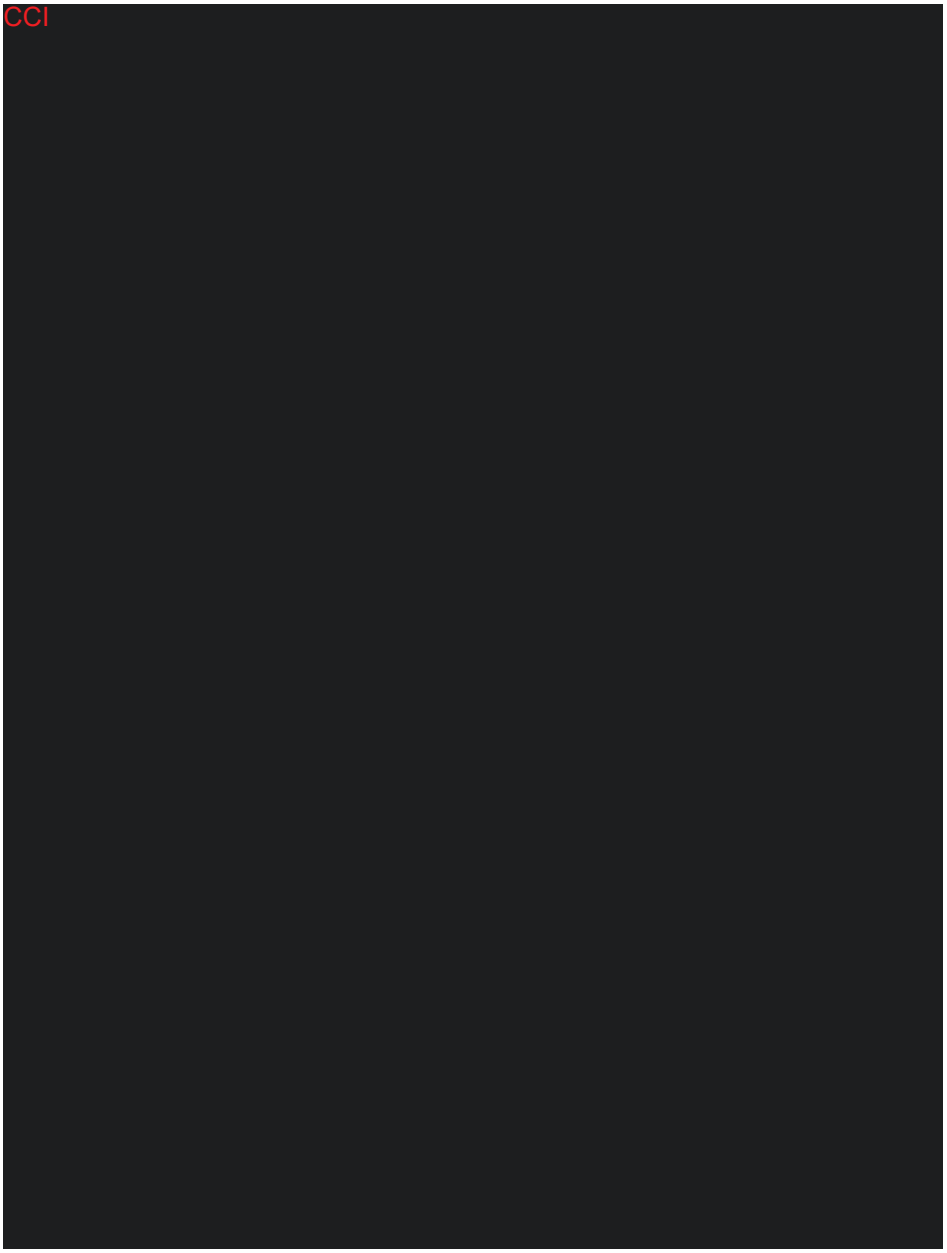
The following drugs are known to have the risk of Torsade de Pointes due to QTc prolongation and their current use in combination with glasdegib is not recommended. If any of these drugs are considered to be medically necessary, then they should be used with caution in combination with glasdegib.

Generic Name	Drug Class	Therapeutic Use	Route
Aclarubicin (Only on Non US Market)	Anti-cancer	Cancer	injection
Amiodarone	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia	oral
Arsenic trioxide	Anti-cancer	Leukemia	injection
Astemizole (Removed from Market)	Antihistamine	Allergic rhinitis	oral
Azithromycin	Antibiotic	Bacterial infection	oral, injection
Bepridil (Removed from Market)	Anti-anginal	Heart pain	oral
Chloroquine	Anti-malarial	Malaria infection	oral
Chlorpromazine	Anti-psychotic/ Anti-emetic	Schizophrenia/nausea Many others	oral, injection, suppository
Cilostazol	Phosphodiesterase 3 inhibitor	Intermittent claudication	oral
Ciprofloxacin	Antibiotic	Bacterial Infection	oral, injection
Cisapride (Removed from Market)	GI stimulant	Increase GI motility	oral
Citalopram	Anti-depressant, SSRI	Depression	oral
Clarithromycin	Antibiotic	Bacterial infection	oral, inhaled
Cocaine	Local anesthetic	Anesthesia (topical)	oral, nasal
Disopyramide	Anti-arrhythmic	Abnormal heart rhythm	Oral, injection
Dofetilide	Anti-arrhythmic	Abnormal heart rhythm	oral
Domperidone Only on Non US market	Anti-emetic	Nausea, vomiting	oral, injection, suppository
Donepezil	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)	oral
Dronedarone	Anti-arrhythmic	Atrial Fibrillation	oral
Droperidol	Anti-psychotic/ Anti-emetic	Anesthesia adjunct, nausea	injection
Erythromycin	Antibiotic	Bacterial infection; increase GI motility	oral, injection

Generic Name	Drug Class	Therapeutic Use	Route
Escitalopram	Anti-depressant, SSRI	Major depression/ Anxiety disorders	oral
Flecainide	Anti-arrhythmic	Abnormal heart rhythm	oral
Fluconazole	Anti-fungal	Fungal infection	oral, injection
Gatifloxacin (Removed from Market)	Antibiotic	Bacterial infection	oral, injection
Grepafloxacin (Removed from Market)	Antibiotic	Bacterial infection	oral
Halofantrine (Only on Non US market)	Anti-malarial	Malaria infection	oral
Haloperidol	Anti-psychotic	Schizophrenia, agitation	oral, injection
Ibogaine (Only on Non US market)	Psychedelic	Narcotic addiction, unproven	oral
Ibutilide	Anti-arrhythmic	Abnormal heart rhythm	injection
Levofloxacin	Antibiotic	Bacterial infection	oral, injection
Levomepromazine (methotrimeprazine) (Only on Non US Market)	Anti-psychotic	Schizophrenia	oral, injection
Levomethadyl (Removed from Market)	Opiate	Narcotic dependence	oral
Mesoridazine (Removed from Market)	Anti-psychotic	Schizophrenia	oral
Methadone	Opiate	Pain control, narcotic dependence	oral, injection
Moxifloxacin	Antibiotic	Bacterial infection	oral, injection
Ondansetron	Anti-emetic	Nausea, vomiting	oral, injection
Oxaliplatin	Anti-cancer	Cancer	injection
Papaverine HCl (Intra-coronary)	Vasodilator, Coronary	Diagnostic adjunct	injection
Pentamidine	Anti-fungal	Pneumocystis pneumonia	injection, inhaled
Pimozide	Anti-psychotic	Tourette's tics	oral
Probucol (Removed from Market)	Antilipemic	Hypercholesterolemia	oral
Procainamide	Anti-arrhythmic	Abnormal heart rhythm	injection
Propofol	Anesthetic, general	Anesthesia	injection
Quinidine	Anti-arrhythmic	Abnormal heart rhythm	oral, injection

Generic Name	Drug Class	Therapeutic Use	Route
Roxithromycin (Only on Non US market)	Antibiotic	Bacterial infection	oral
Sevoflurane	Anesthetic, general	Anesthesia	inhaled
Sotalol	Anti-arrhythmic	Abnormal heart rhythm	oral
Sparfloxacin (Removed from market)	Antibiotic	Bacterial infection	oral
Sulpiride (Only on Non US market).	Anti-psychotic, atypical	Schizophrenia	Oral, inhaled
Terfenadine (Removed from market)	Antihistamine	Allergic rhinitis	oral
Terlipressin (Only on Non US market)	Vacoconstrictor	Septic shock	injection
Terodiline (Only on Non US market)	Muscle relaxant	Bladder spasm	oral
Thioridazine	Anti-psychotic	Schizophrenia	oral
Vandetanib	Anti-cancer	Thyroid cancer	oral

US = United States.
Source: Credible Meds.org (http://crediblemeds.org/healthcare-providers/drug-list/?rf=All). TdP risk category filtered on Drugs with known TdP risk. Accessed 26 October 2018.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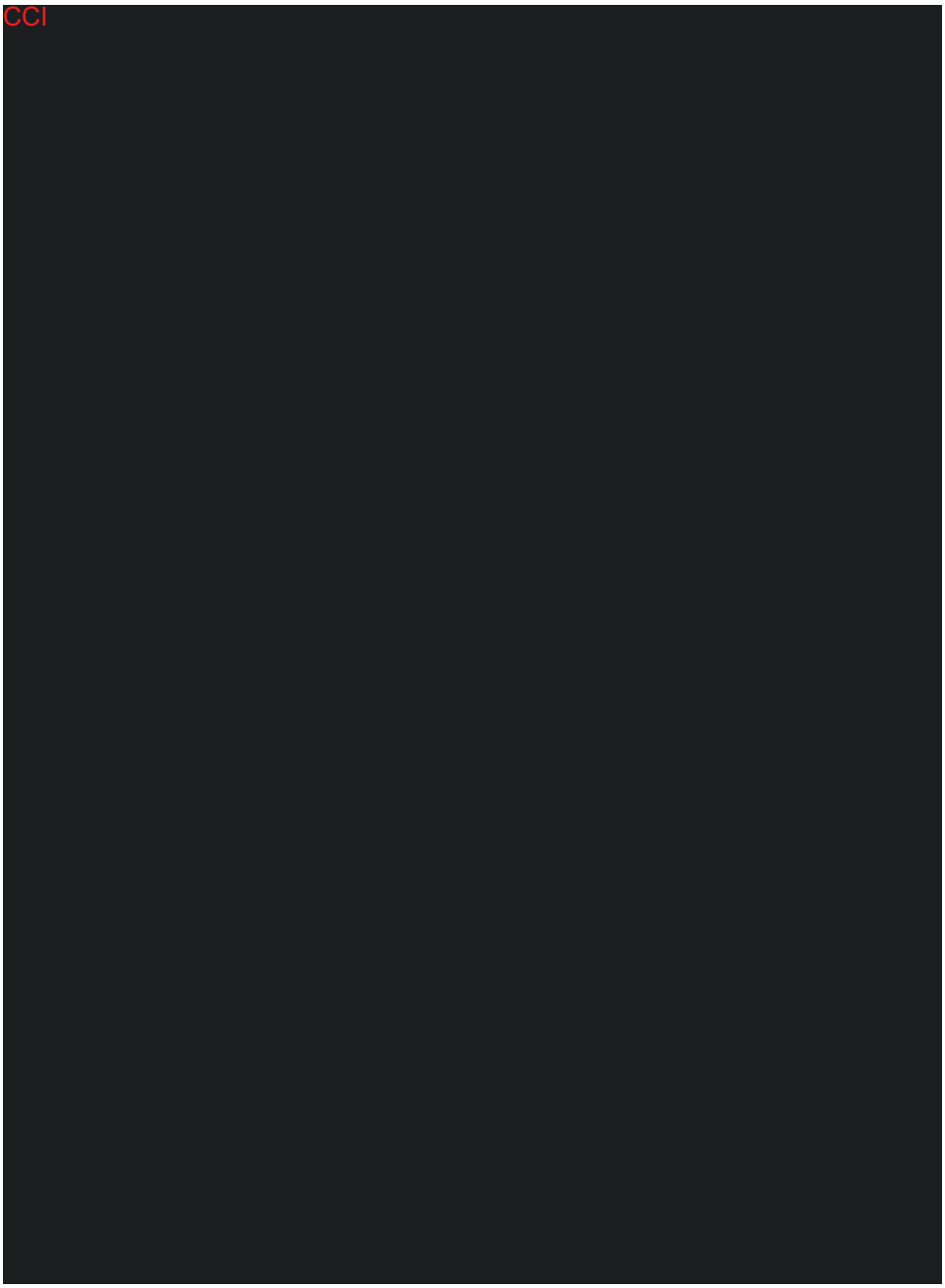

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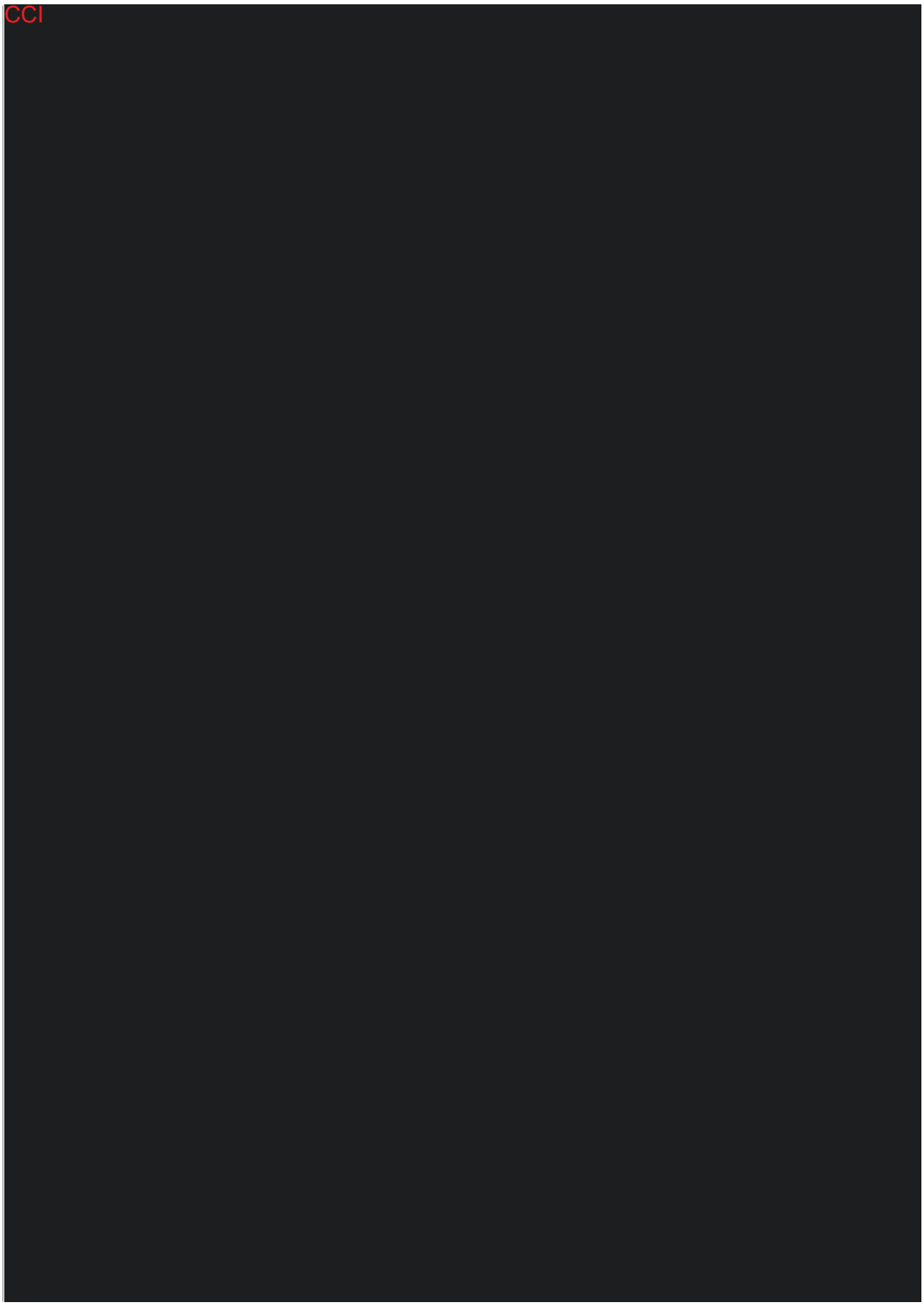
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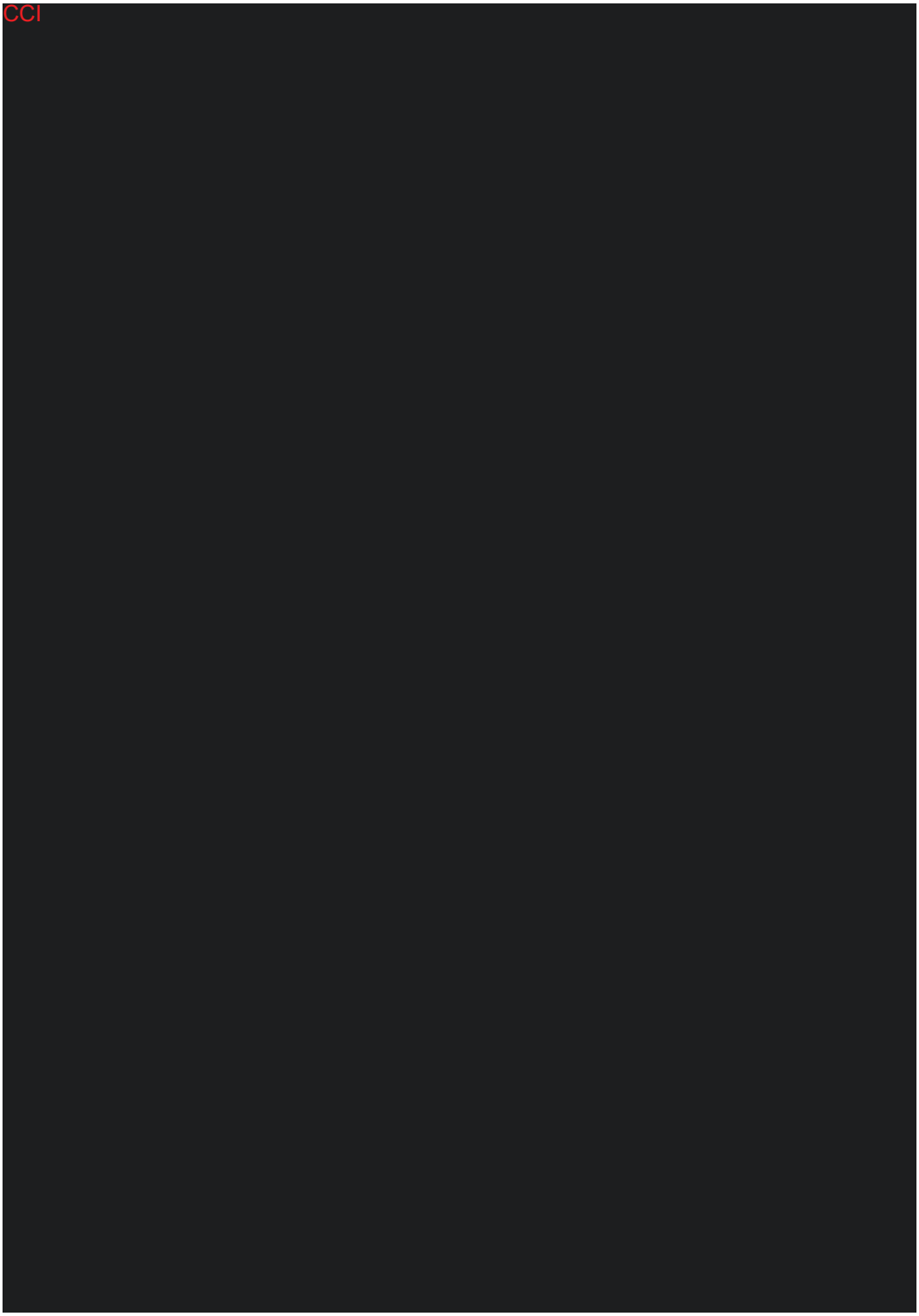

Appendix 14. 2017 ELN Risk Stratification by Genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.

†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.[57-59,77]

‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]

¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

#*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.[37,66-69]

Appendix 15. 2017 Recommended staging and grading of acute GVHD

Table 1 Recommended staging and grading of acute GVHD

	Extent of organ involvement		
	Skin	*Liver*	*Gut*
Stage			
1	Rash on <25% of skin[a]	Bilirubin 2–3 mg/dl[b]	Diarrhea >500 ml/day[c] or persistent nausea[d]
2	Rash on 25–50% of skin	Bilirubin 3–6 mg/dl	Diarrhea >1000 ml/day
3	Rash on >50% of skin	Bilirubin 6–15 mg/dl	Diarrhea >1500 ml/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1–2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	–	Stage 2–3 or	Stage 2–4
IV[f]	Stage 4 or	Stage 4	–

[a]Use 'Rule of Nines' or burn chart to determine extent of rash
[b]Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented
[c]Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Gut staging criteria for pediatric patients was not discussed at the Consensus Conference. Downgrade one stage if an additional cause of diarrhea has been documented.
[d]Persistent nausea with histologic evidence of GVHD in the stomach or duodenum
[e]Criteria for grading given as minimum degree of organ involvement required to confer that grade
[f]Grade IV may also include lesser organ involvement but with extreme decrease in performance status

Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone marrow transplantation* 1995; **15**(6): 825-8.

Appendix 16. France Appendix

This appendix applies to study sites located in France.

1. GCP Training.

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product.

No subjects or third-party payers will be charged for investigational product.

3. Inspections.

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

4. Record Retention.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

5. Urgent Safety Measures.

The investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

6. Termination Rights.

7. Pfizer retains the right to discontinue development of <investigational product> at any time.

8. Studies Involving Human Cell, Tissue, and/or Organ Transplants.

9. The investigator agrees to abide by the ethical principles set forth in the World Health Organization's Guiding Principles for Human Cell, Tissue and Organ Transplantation (WHA63.22), http://www.who.int/transplantation/en/ with regard to the study.